ESC Congress 2018 In Review

Official peer-reviewed highlights

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Main Edition

In This Issue

Highlights of the 2018 ESC Clinical Practice Guidelines

The European Society of Cardiology revealed 4 new guideline updates developed by expert task forces covering the topics of syncope, cardiovascular diseases during pregnancy, arterial hypertension, and myocardial revascularization, and a consensus document on the fourth universal definition of myocardial infarction. The evidence base supporting the guidelines are summarised, and valuable clinical decision-making tools for practicing clinicians are provided.

Also

- Strategies for Secondary Prevention
- Clinical Trial Highlights
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ESC
European Society of Cardiology

Dear Colleagues,

In this issue of *ESC Congress 2018 in Review*, we are delighted to share with you peer-reviewed highlights of the European Society of Cardiology Congress 2018 held in Munich, Germany. Over the five days of the congress – in addition to a rich educational programme - 12 Basic & Translational Science Hot Line presentations, 35 Late Breaking Clinical Trial presentations, 15 Clinical Trial Updates, 30 Late-Breaking Registry Results, 4 new ESC Clinical Practice Guidelines, and 4,461 abstracts were presented. The congress spotlight was 'Valvular Heart Disease' to place a special emphasis on the substantial growth in this area over the past decade. Some new features added to the Congress this year included a track called 'Cardiology in 4 Days', which covered the entire field of cardiology with focused lectures given by leading experts; the expansion of the successful 'Expert Advice' sessions; and a dedicated lecture hall, the 'Library Room', which provided a unique forum for discussions.

The articles selected for this issue of *ESC Congress 2018 in Review*, the official highlights report for ESC Congress 2018, will summarise the most newsworthy, cutting-edge, and clinically relevant topics presented in Munich. A typical example would be the ATTR-ACT study, in which tafamidis reduced hospitalisations and improved both survival and quality of life in patients with transthyretin amyloid cardiomyopathy. The results of ATTR-ACT, COMMANDER HF, MITRA-fr, and the numerous other trials presented at ESC Congress 2018 will influence cardiovascular care and allow us to better understand diseases and manage patients.

New ESC Clinical Practice Guidelines were presented on the diagnosis and management of syncope, the management of cardiovascular diseases during pregnancy, myocardial revascularisation (in conjunction with European Association for Cardio-Thoracic Surgery), and management of arterial hypertension (in conjunction with European Society of Hypertension); with dedicated sessions to help attendees understand the underlying science that support the recommendations and the impact of the new guidelines on their own clinical practice.

We are confident that the articles in this edition of *ESC Congress 2018 in Review* will be useful for your clinical practice. Please also be reminded that ESC 365, presenting all congress resources in one online library, provides access to all abstracts, slides and presentations, along with ESC TV interviews and other material from ESC Congress 2018. To access this unique source of up-to-date information, visit us online at www.escardio.org/365.

We hope you will enjoy this issue of *ESC Congress 2018 in Review* and look forward to seeing you in Paris for ESC Congress 2019. For more information, please visit www.escardio.org/ESC2019.

Professor Stephan Achenbach, FESC
Chairman, ESC Congress Programme Committee 2016-2018

Dear Practitioner,

We are pleased to share with you highlights from the European Society of Cardiology (ESC) Congress 2018 held in Munich, Germany.

The featured article provides a topline summary of the 4 new ESC Clinical Practice Guideline updates released during the congress covering myocardial revascularisation, cardiovascular diseases during pregnancy, arterial hypertension, and syncope, as well as the 4th universal definition of MI.

Several highly anticipated clinical trials were presented at ESC Congress 2018. The ATTR-ACT study investigated tafamidis as a treatment for wild-type transthyretin amyloid cardiomyopathy and found that it improved both survival and quality of life, and reduced hospitalisations in these patients for whom the average survival is 3-5 years after diagnosis and there are no currently approved therapies. The CAMELLIA-TIMI 61 study examined the safety and efficacy of a weight-loss drug (lorcaserin) in overweight or obese patients. Results showed that adding lorcaserin to diet and exercise resulted in sustained weight loss compared with placebo without increasing the risk for MACE. Two highly anticipated trials of aspirin for primary CV prevention (ARRIVE and ASCEND) suggest that aspirin may be of benefit in patients with diabetes, but is accompanied by increased gastrointestinal bleeding and its role in moderate risk non-diabetics is uncertain. Results from two studies of rivaroxaban failed to show significant clinical benefits. In MARINER, rivaroxaban 10 mg daily post discharge did not significantly reduce symptomatic venous thromboembolism (VTE) or VTE-related death versus placebo in medically-ill patients, although unexpectedly low event rates reduced the ability to demonstrate a statistical difference given the observed 24% relative risk reduction. In COMMANDER HF, rivaroxaban 2.5 mg twice daily did not significantly reduce the composite of death, MI, or stroke compared with placebo in patients with ischaemic cardiomyopathy in sinus rhythm.

In addition to guideline updates and the results from Hot Line sessions, you will also find information on selected areas of cardiovascular medicine including innovative strategies for secondary prevention and antithrombotic therapy in patients with AF + ACS.

We hope that you find the articles and practical perspectives that are contained in the pages of this issue of *ESC Congress 2018 in Review* helpful in integrating this new information into your clinical practice.

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Main Session

Late-Breaking Science

Selected Content

ESC European Society of Cardiology

Highlights of the 2018 ESC Clinical Practice Guidelines

Written by **Lisa Buttle**

The European Society of Cardiology (ESC) revealed 4 new guideline updates developed by expert task forces covering the topics of syncope, cardiovascular diseases (CVD) during pregnancy, arterial hypertension, and myocardial revascularisation, and a consensus document on the fourth universal definition of myocardial infarction (MI). The guidelines summarise the evidence base on these topics, and provide a valuable clinical decision-making tool for practicing clinicians. All guidelines can be accessed from the ESC website (www.escardio.org/guidelines) and the ESC Pocket Guidelines App.

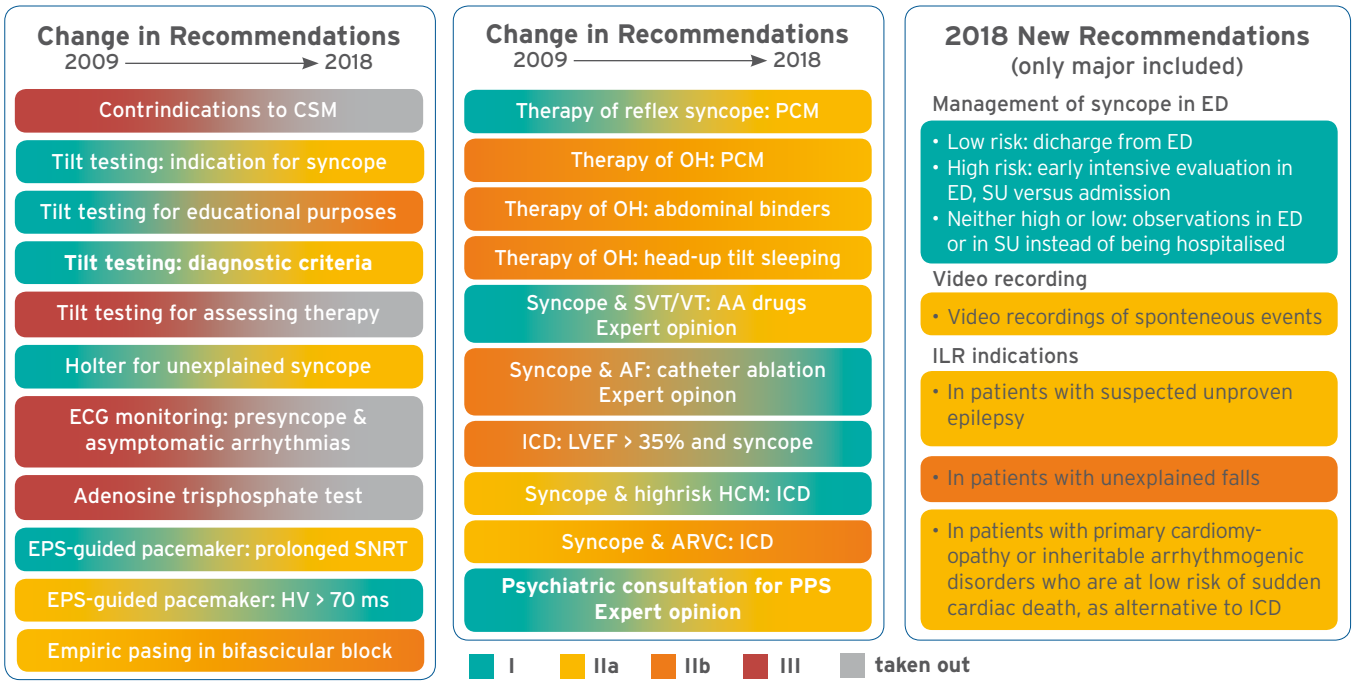
Syncope

The 2018 ESC Guidelines for the Diagnosis and Management of Syncope [Brignole M et al. *Eur Heart J*. 2018] were developed with the special contribution of the European Heart Rhythm Association (EHRA) and presented by Javier Moreno, MD, PhD, Hospital Universitario Ramón y Cajal, Madrid, Spain.

The 2018 guidelines contain a number of updated recommendations and important new and revised concepts, which are summarised in Figure 1, notably with the downgrade of Tilt testing, and the upgrade to class I recommendation for catheter ablation when syncope occurs with atrial fibrillation (AF).

Risk stratification in the emergency department at the initial presentation of syncope is essential to determine whether admission and subsequent investigations are needed, and the revised recommendations for management based upon risk are shown in Figure 2. Examples of high-risk features include new onset of chest discomfort, shortness of breath, headache, abdominal pain, sudden onset of palpitations followed by syncope, or a history of structural or coronary artery disease.

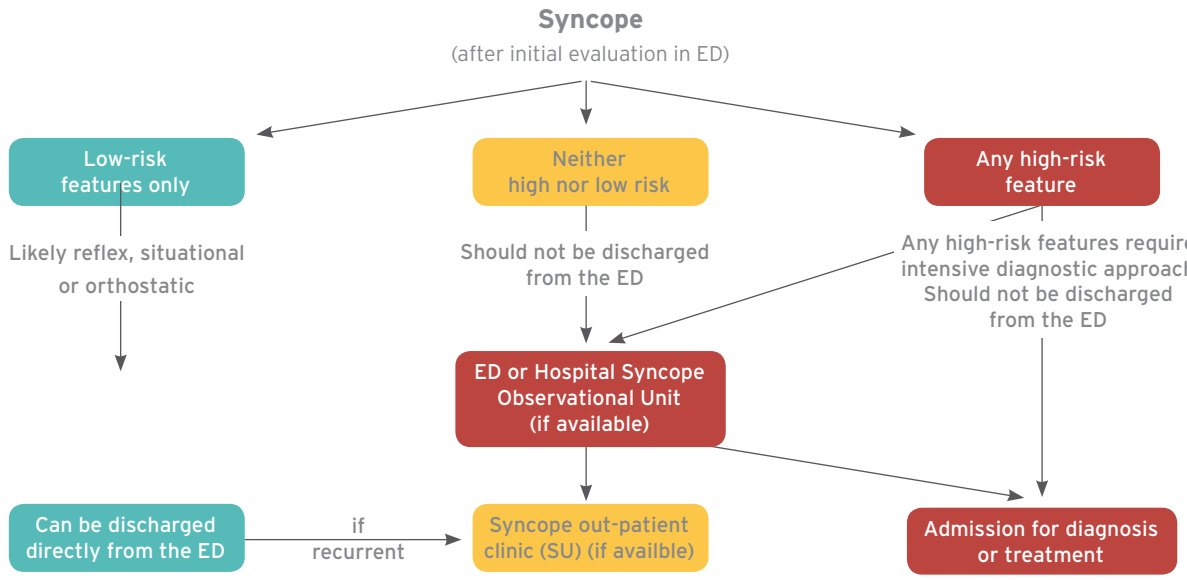
Figure 1. What Is New in the 2018 Syncope Guidelines



AA, antiarrhythmic; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CSM, carotid sinus massage; ECG, electrocardiogram; ED, emergency department; LVEF, left ventricular ejection fraction; EPS, electrophysiological study; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; OH, orthostatic hypotension; PCM, physical counter-pressure manoeuvres; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; SNRT, sinus node recovery time; SU, syncope unit; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Reprinted from Brignole M et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy037. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Figure 2. Emergency Department Risk Stratification Flow Chart



ED, emergency department; SU, syncope unit.

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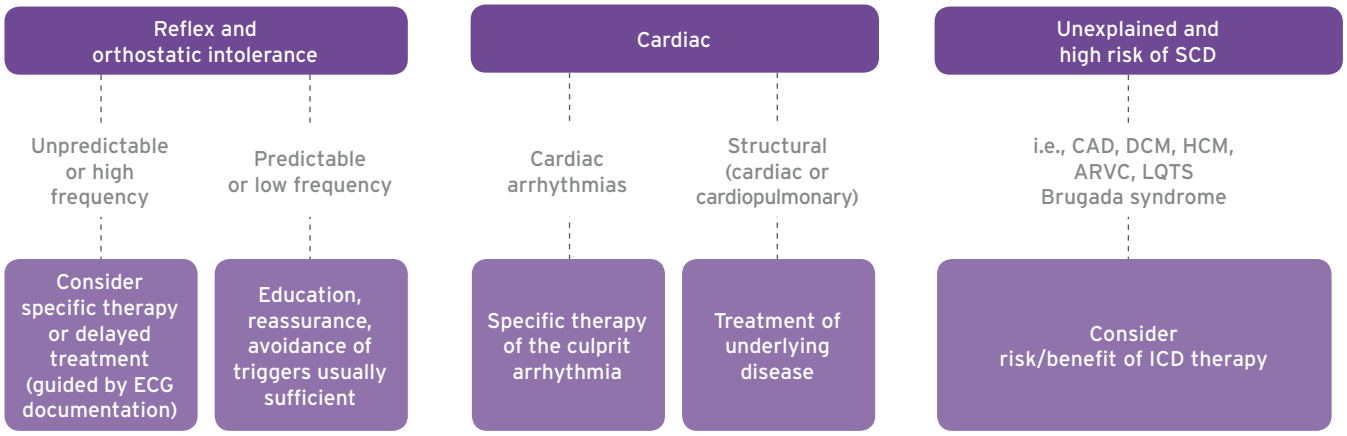
Subsequent investigations of syncope may include prolonged electrocardiographic monitoring, electrophysiology studies, and exercise testing; indications for use of these investigative techniques are included in the full guidelines. A new recommendation suggests the use of video recording of spontaneous events either at home or in hospital; video recording offers pathophysiological insights into syncope and may allow complex events to be diagnosed. Treatment recommendations are based on the identification of specific causes of syncope, wherever possible, and treatment principles are outlined in Figure 3. A new addition to the 2018 guidelines is a chapter focusing on organisational aspects of care, and outlining key drivers for efficient operation of the Syncope Unit.

Cardiovascular Diseases During Pregnancy

The 2018 ESC Guidelines for the Management of Cardiovascular Diseases during Pregnancy [Regitz-Zagrosek V et al. *Eur Heart J*. 2018] were presented by Christi Deaton, PhD, RN, University of Cambridge School of Clinical Medicine, United Kingdom. Since the 2012 guidelines were published, new evidence has accumulated on diagnostic techniques, risk assessment, and the use of CV drugs; full details of these topics are provided in the 2018 update along with new user-friendly summaries in each section highlighting recommendations and remaining 'gaps in the evidence'. New concepts introduced in the 2018 update are listed in Table 1.

Figure 3. General Framework for Treatment of Syncope and the Identification of Specific Mechanisms



ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; DCM, dilated cardiomyopathy; ECG, electrocardiographic; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; SCD, sudden cardiac death.

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Table 1. New Concepts in the 2018 ESC Guidelines on Cardiovascular Diseases in Pregnancy

New concepts
Enforcing mWHO classification of maternal risk.
Introduction of the pregnancy heart team.
More attention for assisted reproductive therapy.
Discussion of the use of bromocriptine in peripartum cardiomyopathy.
Introduction of specific levels of surveillance based on low/medium/high risk for arrhythmia with haemodynamic compromise at delivery.
New information on pharmacokinetics in pregnancy, more detailed information on pharmacodynamics in animal experiments on all drugs.
Perimortem caesarean section is discussed.
Advice on contraception and the termination of pregnancy in woman with cardiac disease is now provided.

mWHO, modified World Health Organization.

Reprinted from Regitz-Zagrosek V et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy340. By permission of Oxford University Press on behalf of the European Society of Cardiology.

All women with known cardiac or aortic disease who wish to become pregnant should receive prepregnancy counseling to facilitate informed maternal decision making. To assess maternal risk of cardiac complications during pregnancy, the ESC Task Force recommends the modified World Health Organization (mWHO) disease-specific risk classification tool. The general principles of the mWHO classification, and follow-up and management during pregnancy are presented in Table 2. Prepregnancy counseling as well as management during pregnancy and around delivery should be conducted in an expert centre by a multidisciplinary team – the pregnancy heart team – including a cardiologist, obstetrician, anaesthetist, and other specialists.

Peripartum cardiomyopathy (PPCM) is a rare condition that may cause severe complications in pregnancy. PPCM presents with HF secondary to left ventricular (LV)

Table 2. Modified World Health Organization Classification of Maternal Cardiovascular Risk

	mWHO I	mWHO II	mWHO II–III	mWHO III	mWHO IV
Diagnosis (if otherwise well and uncomplicated)	Small or mild – pulmonary stenosis – patent ductus arteriosus – mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated	Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias (supraventricular arrhythmias) Turner syndrome without aortic dilatation	Mild LV impairment (EF > 45%) Hypertrophic cardiomyopathy Native or tissue valve disease not considered WHO I or IV (mild mitral stenosis, moderate aortic stenosis) Marfan or other HTAD syndrome without aortic dilatation Aorta < 45 mm in bicuspid aortic valve pathology Repaired coarctation Atrioventricular septal defect	Moderate LV impairment (EF 30–45%) Previous peripartum cardiomyopathy without any residual LV impairment Mechanical valve Systemic right ventricle with good or mildly decreased ventricular function Fontan circulation. If otherwise the patient is well and the cardiac condition uncomplicated Unrepaired cyanotic heart disease Other complex heart disease Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve, Turner syndrome ASI 20–25 mm/m^2, tetralogy of Fallot < 50 mm) Ventricular tachycardia	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (EF < 30% or NYHA class III–IV) Previous peripartum cardiomyopathy with any residual LV impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortic dilatation (> 45 mm in Marfan syndrome or other HTAD, > 50 mm in bicuspid aortic valve, Turner syndrome ASI > 25 mm/m^2, tetralogy of Fallot > 50 mm) Vascular Ehlers–Danlos Severe (re)coarctation Fontan with any complication
Risk	No detectable increased risk of maternal mortality and no/mild increased risk in morbidity	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity	Significantly increased risk of maternal mortality or severe morbidity	Extremely high risk of maternal mortality or severe morbidity
Maternal cardiac event rate	2.5–5%	5.7–10.5%	10–19%	19–27%	40–100%
Counselling	Yes	Yes	Yes	Yes: expert counselling required	Yes: pregnancy contraindicated: if pregnancy occurs, termination should be discussed
Care during pregnancy	Local hospital	Local hospital	Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease
Minimal follow-up visits during pregnancy	Once or twice	Once per trimester	Bimonthly	Monthly or bimonthly	Monthly
Location of delivery	Local hospital	Local hospital	Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease

ASI, aortic size index; EF, ejection fraction; HTAD, heritable thoracic aortic disease; LV, left ventricular; mWHO, modified World Health Organization; NYHA, New York Heart Association.

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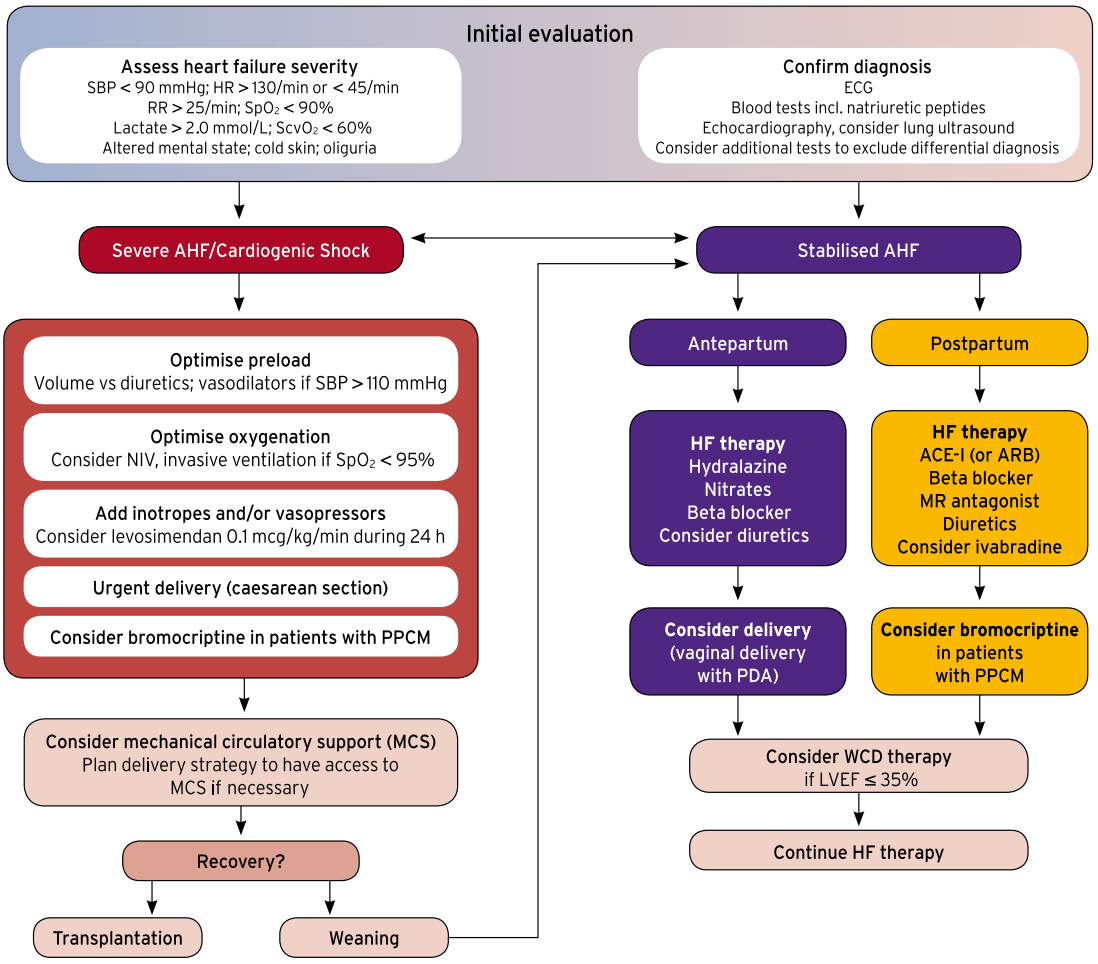
Figure 4. Management of Acute Heart Failure During/After Pregnancy



ACE-I, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; ECG, electrocardiogram; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MR, mineralocorticoid receptor; NIV, non-invasive ventilation; PDA, peridural analgesia; PPCM, peripartum cardiomyopathy; RR, respiratory rate; SBP, systolic blood pressure; $ScvO_2$, central venous oxygen saturation; SpO_2, peripheral oxygen saturation; WCD, wearable cardioverter-defibrillator.

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systolic dysfunction towards the end of pregnancy and in the months following delivery. The use of bromocriptine has emerged as a new concept for the management of PPCM and HF in pregnancy in the 2018 guidelines. The addition of bromocriptine to standard HF therapy may be considered to stop lactation and improve LV recovery and clinical outcome in women with acute severe PPCM, and should be accompanied by anticoagulation therapy. Patients with symptoms and signs of acute heart failure (AHF) should be evaluated according to AHF guidelines, and the management goals are similar to non-pregnant HF while avoiding fetotoxic drugs during pregnancy (Figure 4).

For all CV drugs used in pregnancy, new and extensive safety data are included in the full 2018 guidelines update. The principles of drug treatment of CV diseases during pregnancy are outlined in Table 3.

Table 3. Recommendations for Drug Use in Pregnancy

Recommendations	Class[a]	Level[b]
Before pharmacological treatment in pregnancy is started, it is recommended to check full guidelines for clinical safety data.	I	C
In the absence of clinical safety data, it is recommended to check the electronic drug table (www.safefetus.com) for pre-clinical safety data.	I	C
In the absence of adequate human safety data, decision-making should be based on individual drug efficacy and safety profiles, and the available animal data, and the decision must be made together with the patient.	IIa	C
Decision-making based on former FDA categories alone is no longer recommended.	III	C

[a]Class of recommendation; [b]Level of evidence. FDA, US Food and Drug Administration.

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Figure 5. Classification of Hypertension Stage According to Blood Pressure, Presence of Cardiovascular Risk Factors, Hypertension-mediated Organ Damage, or Comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥ 180 or DBP ≥ 110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥ 3 risk factors	Low to Moderate risk	Moderate to high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High risk to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; HMOD, hypertension-mediated organ damage; SBP, systolic blood pressure; SCORE, Systematic Coronary Risk Evaluation.

Reprinted from Williams B et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy339. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Management of Arterial Hypertension

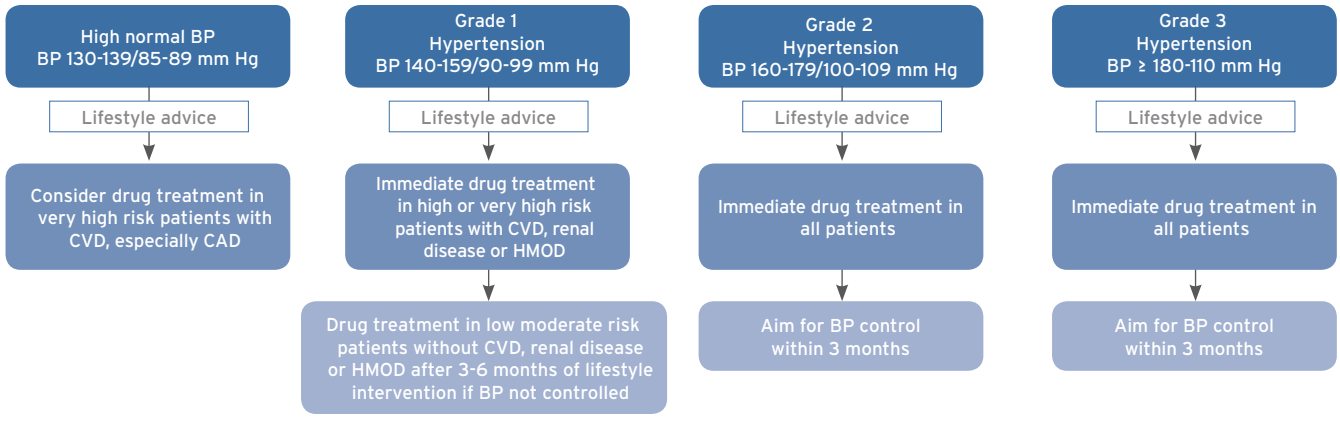
The 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension [Williams B et al. *Eur Heart J*. 2018] were developed in collaboration with the European Society of Hypertension (ESH) and presented by Guy De Backer, MD, PhD, University of Ghent, Belgium. An important shift in the 2018 guidelines is a move away from the sole use of repeat office blood pressure (BP) measurements for diagnosis, with promotion of the use of out-of-office ambulatory or home BP measurements for diagnosis, to detect white coat and masked hypertension, and to monitor BP control.

Global risk stratification is a key message of the 2018 guidelines. The management of hypertension requires formal CV risk assessment, which is recommended with the SCORE model. CV risk can be modified by other risk qualifiers, in particular by the presence of hypertension-mediated organ damage (previously termed 'target organ damage') which should be screened for in hypertensive patients (Figure 5).

For hypertension management, lifestyle adaptations are strongly recommended in all patients and drug treatment is based upon risk assessment and hypertension grade. The 2018 guidelines recommend a more aggressive drug-therapy regimen than the previous guidelines, particularly in the elderly where the biological rather than the chronological age should be considered. The treatment strategy should also take into account fitness, drug tolerance, and total CV risk (Figure 6).

The 2018 Task Force recommends a first treatment target to BP < 140/90 mm Hg in all patients, and if well-tolerated, treated BP should be targeted to ≤ 130/80 mm Hg in most patients, depending on a patient's age and comorbidities, although in some groups the evidence is less compelling. Regarding treatment selection, the 2018 guidelines make two new recommendations: to start treatment in most patients with 2 drugs not 1 (excluding an ACE + ARB combination), and the preferred use of single pill combination therapy to improve adherence to treatment. Detecting poor adherence is

Figure 6. Initiation of Blood Pressure-Lowering Treatment at Different Initial Office Blood Pressure Levels



BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; HMOD, hypertension-mediated organ damage.

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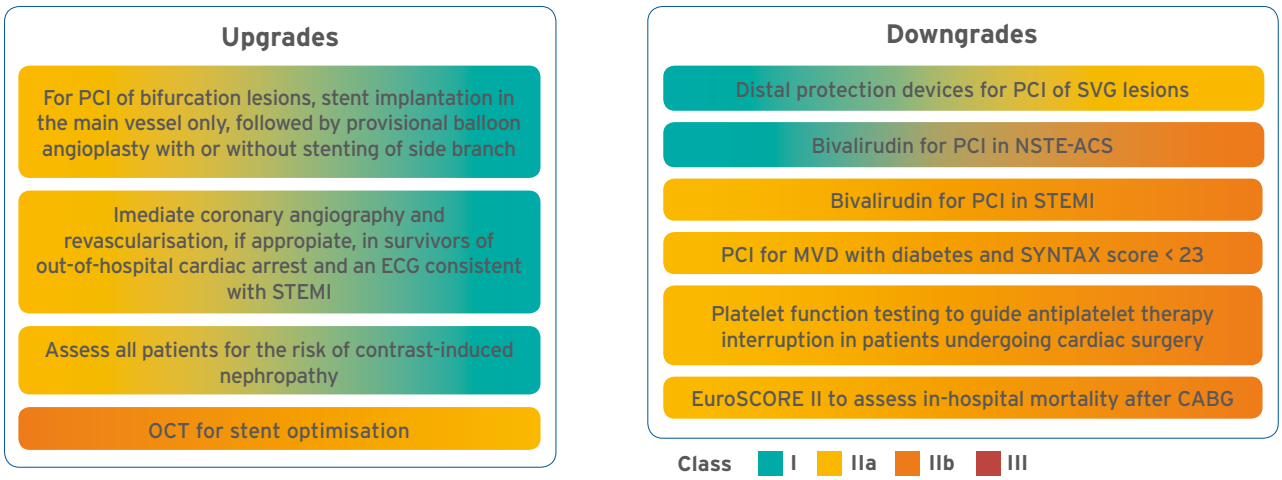
Figure 7. New Recommendations in the 2018 ESC/EACTS Guidelines on Myocardial Revascularization



CABG, coronary artery bypass grafting; ECG, electrocardiogram; MVD, multivessel coronary artery disease; NSTE-ACS, non-ST elevation-acute coronary syndrome; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SVG, saphenous vein grafts.

Reprinted from Neumann F-J et al. 2018 ESC/EACTS Guidelines on Myocardial Revascularization. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy394. By permission of Oxford University Press on behalf of the European Society of Cardiology.

strongly emphasised in the new guidelines; nurses and pharmacists should play a key role in patient education and support, which will facilitate adherence. More details on treatment and a new chapter on hypertension in specific circumstances can be found in the full 2018 guidelines.

Myocardial Revascularisation

The 2018 ESC/EACTS Guidelines on Myocardial Revascularization [Neumann F-J et al. *Eur Heart J*. 2018] were developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI). New recommendations included in the 2018 guidelines are listed in Figure 7.

The guidelines overview was presented by William Wijns, MD, PhD, National University of Ireland, Galway, Ireland, who identified four essential take home messages of the 2018 guidelines:

1) Decision making for stented percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be based on combined evaluation of anatomy and physiology (non-invasive or invasive testing; Table 4).
2) Evaluation of the extent of coronary artery disease (CAD) by SYNTAX score (www.syntaxscore.com) is essential when choosing between revascularisation modalities (CABG or PCI).
3) The presence of diabetes is an important decision modifier by itself.
4) The probability of achieving complete revascularisation is of extreme prognostic importance.

Table 4. Aspects to be Considered by the Heart Team for Decision Making Between PCI and CABG Among Patients With Stable Multivessel and/or Left Main Coronary Artery Disease

	Favours PCI	Favours CABG
Clinical characteristics	- Presence of severe co-morbidity (not adequately reflected by scores) - Advanced age/frailty/ reduced life expectancy - Restricted mobility and conditions that affect the rehabilitation process	- Diabetes - Reduced LV function (EF ≤ 35%) - Contraindication to DAPT - Recurrent diffuse in-stent restenosis
Anatomical and technical aspects	- MVD with SYNTAX score 0–22 - Anatomy likely resulting in incomplete revascularisation with CABG due to poor quality or missing conduits - Severe chest deformation or scoliosis - Sequelae of chest radiation Porcelain aorta[a]	- MVD with SYNTAX score ≥ 23 - Anatomy likely resulting in incomplete revascularisation with PCI - Severely calcified coronary artery lesions limiting lesion expansion
Need for concomitant interventions		- Ascending aortic pathology with indication for surgery - Concomitant cardiac surgery

[a]Consider no-touch off-pump CABG in case of porcelain aorta.
CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; EF, ejection fraction; LV, left ventricular; MVD, multivessel coronary artery disease; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

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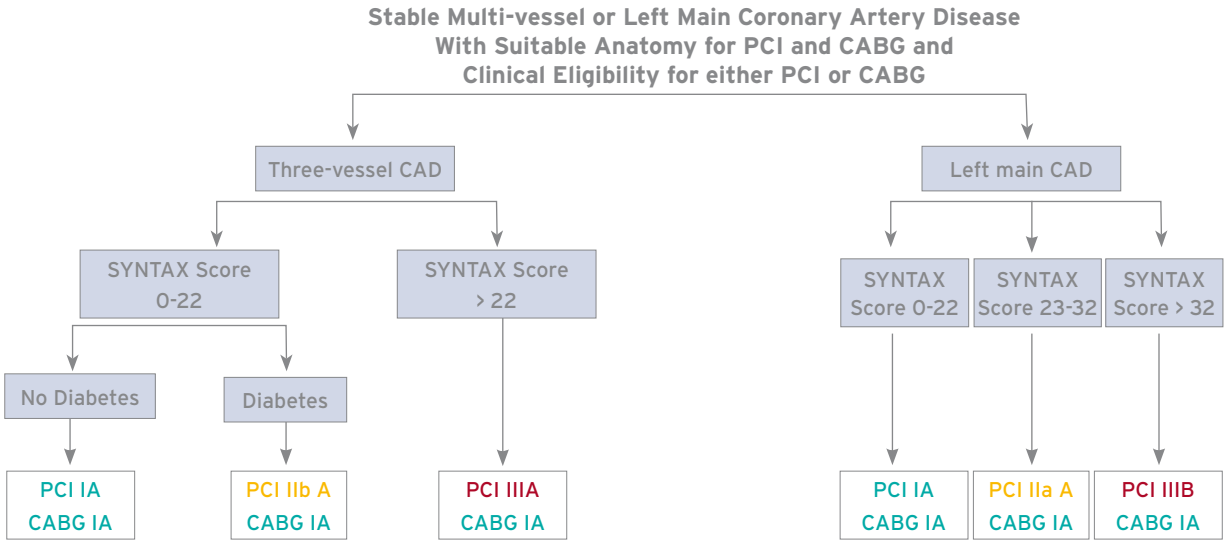
Figure 8. Algorithm to Guide the Choice of Revascularisation Procedure Across Major Categories in Patients With Multivessel or Left Main Coronary Artery Disease



Class recommendations correspond to the 2018 ESC/EACTS Guidelines on Myocardial Revascularization.
CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

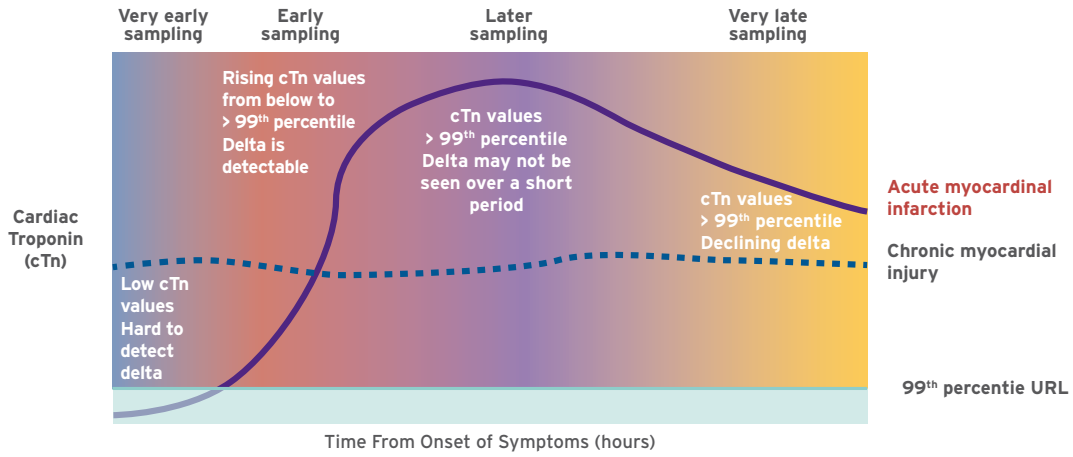
Reprinted from Windecker S et al. Considerations for the choice between CABG and PCI as revascularisation strategies in major categories of patients with stable multivessel coronary artery disease. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy532. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Considerations for the choice between CABG and PCI as revascularization strategies are further discussed by Windecker et al. in an article accompanying the 2018 guidelines [Windecker S et al. *Eur Heart J*. 2018]. This article expands upon the guidelines chapter on revascularisation in stable CAD and presents an algorithm to guide choice of revascularisation (Figure 8).

Universal Definition of Myocardial Infarction

The Fourth Universal Definition of MI (2018) [Thygesen K et al. *Eur Heart J*. 2018] was developed by a joint Task Force of the ESC, American College of Cardiology (ACC), American Heart Association (AHA), and World Heart Federation (WHF), and was presented by David Hasdai, MD, Rabin Medical Center, Tel Aviv, Israel. One of the key reasons for the Fourth Universal Definition of MI document is the introduction and adoption of high-sensitivity troponin assays to define MI. A chapter identifies strict technical criteria on the use of troponin assays, highlights caveats and advantages of their use, and discusses troponin level kinetics and the influence of timing on assay measurement (Figure 9).

Figure 9. Early Cardiac Troponin Kinetics in Patients After Acute Myocardial Injury Including Acute Myocardial Infarction



cTn, cardiac troponin; URL, upper reference limit.

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An important new concept in the Fourth Universal Definition of MI is the differentiation between myocardial injury and MI, which is defined in Table 5. There are many conditions that lead to increased troponin level denoting myocardial injury (e.g., HF, CM). Only when there is clinical evidence of myocardial ischaemia and myocardial injury can MI be diagnosed. Figure 10 provides a model for interpretation of myocardial injury versus MI in clinical scenarios. The Fourth Universal Definition of MI includes further details on the differentiation between type 1 MI and type 2 MI, which is a cause of some confusion in clinical practice. A framework is provided for determining type 2 MI considering the clinical context and mechanisms attributable to acute MI.

The Fourth Universal Definition of MI includes a chapter on the use of imaging techniques that can be employed to diagnose and characterise myocardial injury and MI. For example, magnetic resonance imaging can detect evidence of scarring which is apparent in MI, but can also be used to rule out a diagnosis of MI and identify other causes of myocardial injury (e.g., Takotsubo syndrome, AF); these other scenarios are discussed in new sections in the Fourth Universal Definition of MI.

Table 5. Universal Definitions of Myocardial Injury and Myocardial Infarction

Criteria for Myocardial Injury
The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.
Criteria for Acute Myocardial Infarction (types 1, 2 and 3 MI)
The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following: • Symptoms of myocardial ischaemia; • New ischaemic electrocardiogram (ECG) changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; • Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs). Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI. Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.
Criteria for Coronary Procedure-related Myocardial Infarction (types 4 and 5 MI)
Percutaneous coronary intervention (PCI) related MI is termed type 4a MI. Coronary artery bypass grafting (CABG) related MI is termed type 5 MI. Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following: • New ischaemic ECG changes (this criterion is related to type 4a MI only); • Development of new pathological Q waves; • Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology; • Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolisation. Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria with either revascularisation procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG. Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria. Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.
Criteria for Prior or Silent/Unrecognised Myocardial Infarction
Any one of the following criteria meets the diagnosis for prior or silent/unrecognised MI: • Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes. • Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology. • Patho-anatomical findings of a prior MI.

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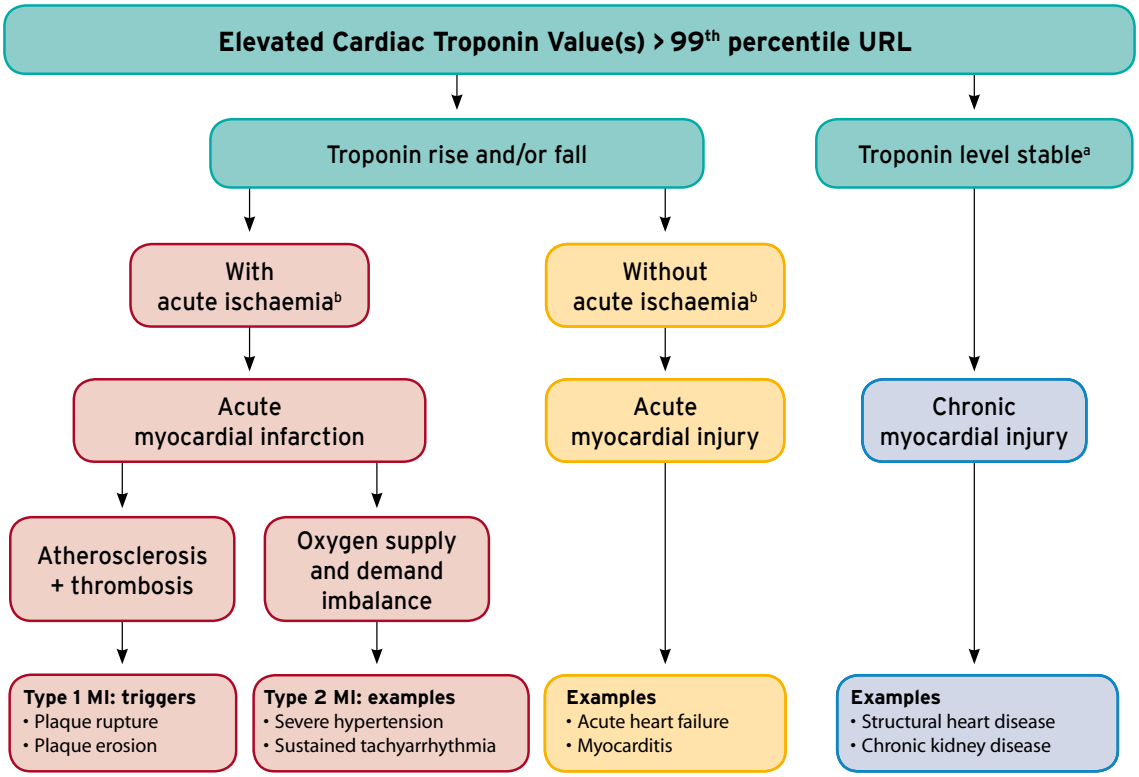
Figure 10. A Model for Interpreting Myocardial Injury



[a]Stable denotes ≤ 20% variation of troponin values; [b]Ischaemia denotes signs and/or symptoms of clinical myocardial ischaemia.
MI, myocardial infarction; URL, upper reference limit.

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Content Ed Net
MEDICOM

The Editors would like to thank the many Members of the ESC Congress 2018 presenting faculty, who generously gave their time to ensure the accuracy and quality of the articles in this publication

No Advantage of Early Invasive Strategy in NSTE-ACS

Written by **Michiel Tent**

Very early invasive coronary evaluation, within 12 hours, does not improve overall long-term clinical outcomes compared with an invasive strategy conducted within 2-3 days in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). In patients with the highest risk, however, very early invasive therapy improves long-term outcomes.

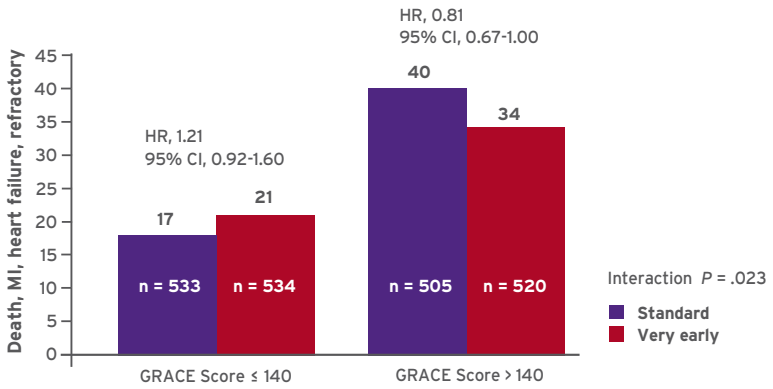
Current guidelines recommend invasive angiography within 24 hours in high-risk patients with NSTE ACS. European Society of Cardiology guidelines define high-risk as a GRACE score > 140, a rise in troponin, or ECG with ischaemia. However, the ideal timing of invasive angiography and revascularisation is unclear. The Very EaRly vs Deferred Invasive evaluation using Computerized Tomography [VERDICT; Kofoed KF et al. *Circulation*. 2018] trial was designed to test the hypothesis that very early invasive coronary angiography (ICA) and possible revascularisation within 12 hours of diagnosis is superior, in terms of clinical outcomes, to an invasive strategy performed within 48-72 hours in patients with NSTE-ACS.

Eligible for inclusion were patients with clinical suspicion of NSTE ACS, electrocardiogram changes indicating new ischaemia, and/or elevated troponin. Excluded were patients with ST-segment elevation myocardial infarction (STEMI) or very high-risk non-STEMI ACS. Participants were randomised 1:1 to coronary angiography within 12 hours of diagnosis (the very early group) or 48-72 hours after diagnosis (the deferred group). Percutaneous coronary intervention (PCI) was the preferred revascularisation strategy; patients not feasible for PCI were allowed coronary artery bypass graft (CABG) surgery. The primary endpoint was a composite of all-cause death, non-fatal recurrent myocardial infarction (MI), hospital admission for refractory myocardial ischaemia, or hospital admission for heart failure.

Thomas Engstrøm, DMSci, PhD, Rigshospitalet, University of Copenhagen, Denmark, presented the results for the 2,147 patients who were randomised. Thirty-two percent had no significant coronary artery disease (CAD). A quarter of patients presented with at least one occluded artery. In the very early group, time to angiography was a median of 4.7 hours compared with 61.6 hours after randomisation in the deferred group. Among patients with significant CAD identified by ICA, revascularisation was performed slightly more often in the very early group (88.4% vs 83.1%).

After a median follow-up of 4.3 years, the composite primary endpoint occurred in 296 patients (27.5%) in the very early group and in 316 (29.5%) in the deferred group (HR, 0.92; 95% CI, 0.78 to 1.08; *P* = .29). Prof. Engstrøm added that in high-risk patients (GRACE score > 140; n = 1,025) a very early invasive treatment strategy lowered the risk of reaching the primary outcome (HR, 0.81; 95% CI, 0.67 to 1.00; *P* for interaction = .023; Figure 1). Risk of nonfatal MI, one of the secondary outcomes, was also significantly lower in the very early group (8.4% vs 11.2%; HR, 0.73; 95% CI, 0.56 to 0.96; *P* = .025); these findings, however, were only hypothesis-generating.

Figure 1. Primary Endpoint Results According to GRACE Risk Score



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Prof. Engstrøm observed that very early invasive angiography is feasible, but logistically challenging and possibly not cost effective. It should, however, be performed in patients that present with symptoms of ACS, elevated troponin, and a high GRACE risk score.

Higher Mortality With FFR-Guided Treatment Choice of Multivessel Disease

Written by **Michiel Tent**

Final results of the FUTURE [FUnctional Testing Underlying Revascularization; NCT0188155] trial showed that the use of fractional flow reserve (FFR) to guide treatment choice in all-comer patients with multivessel disease was associated with more than double the risk of mortality after one year despite decreasing the rate of revascularisation.

Gilles Rioufol, MD, PhD, Hospital Louis Pradel, Bron, France, presented the results and noted that the use of FFR is recommended in the current guidelines for guiding percutaneous coronary intervention (PCI) in patients with multivessel disease who are eligible for PCI [Windecker S et al. *Eur Heart J*. 2014]. The trial was conducted to verify whether FFR may aid in the decision between different treatment strategies – PCI, coronary artery bypass grafting (CABG), or optimal medical treatment (OMT) only – and thereby improve clinical prognosis compared with traditional management.

FUTURE was a multicentre, randomised, prospective, open-label, controlled study in 31 French centres. The primary composite endpoint was all-cause mortality, myocardial infarction (MI), repeat revascularisation, or stroke at one year. Patients with either stable angina or stabilised acute coronary syndrome (ACS) and multivessel disease (> 50% stenosis) were eligible for the study. Eligible patients were randomised to either FFR or angiography. A total of 1,728 patients were to be enrolled, but the trial was prematurely halted after 938 patients had been randomised because of higher rates of all-cause mortality in the FFR group.

Of 938 randomised participants, 31% presented with diabetes, 20% with a history of MI, and 46% with ACS, while 52% had three significant lesions. The average SYNTAX score was 19 in the FFR-guided group and 18 in the angiography-guided group. Overall, 470 of 1,090 lesions (43%) evaluated by FFR had a reading above 0.80.

Prof. Rioufol said global results showed that use of FFR resulted in a lower rate of PCI than did angiography (71% vs 79%; *P* = .002) and in a higher rate of OMT alone (17% vs 9%). The rate of ad hoc PCI was 91% and 90%, respectively. CABG was used in only 12% of patients in both arms.

At 1 year, there was no significant difference in the primary composite endpoint of all-cause mortality, MI, repeat revascularisation, or stroke at 1 year between the FFR- and the angiography-guided group (HR, 0.97; 95% CI, 0.69 to 1.36; *P* = .85) or 2 years (HR, 0.99; 95% CI, 0.75 to 1.30; *P* = .93). In a subgroup analysis, the risk of the primary endpoint was higher in patients randomised to FFR-guided strategy who had a Syntax Score > 32 (HR, 3.32; 95% CI, 0.66 to 16.84) or stable angina (HR, 2.31; 95% CI, 1.02 to 5.22). A safety analysis revealed the risk of all-cause mortality at 1 year was significantly higher in the FFR group (HR, 2.39; 95% CI, 1.05 to 5.43; *P* = .038), after which the trial was prematurely halted; notably, this was not procedure-related.

Prof. Rioufol hypothesised that three factors may explain the excess mortality in the FFR-guided group, including the lower-than-expected rate of CABG in a population of multivessel disease patients; the high rate of PCI in severe patients with a SYNTAX score > 32; and the high rate of ad hoc PCI.

Gastrointestinal and Genitourinary Bleeding May Predict Underlying Cancer

Written by **Phil Vinall**

New data from the COMPASS trial indicates that increased gastrointestinal (GI) and genitourinary (GU) bleeding in patients treated with antithrombotic drugs is associated with GI and GU cancer diagnoses.

GI and GU bleeding may be the first sign of an underlying cancer [Jones R et al. *BMC*. 2007; Ford AC et al. *Gut*. 2008]. In the COMPASS trial, treatment with rivaroxaban compared with aspirin was associated with increased GI, but not GU bleeding [Eikelboom JW et al. *N Engl J Med*. 2017]. Using data from COMPASS, John W. Eikelboom, MD, McMaster University, Hamilton, Ontario, Canada, sought to determine whether GI and GU bleeding were associated with increased rates of new cancer diagnoses in patients treated with rivaroxaban.

The COMPASS trial included 27,395 patients with stable coronary or peripheral arterial disease who were randomised to treatment with rivaroxaban 2.5 mg twice daily plus aspirin, 5 mg rivaroxaban, or 100 mg once daily aspirin. Bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria. A new cancer diagnosis was defined as first-ever, or recurrent cancer from a previous diagnosis in patients whose cancer had been thought to have

been eradicated. The proportion of new cancers before and after bleeding, the association between bleeding and new cancer diagnosis, and rates of cancer diagnosis according to randomised treatment were analysed.

In all, 1,082 new cancers were diagnosed during the trial; 257 (23.8%) of these were diagnosed after bleeding (70 were GI cancers and 62 were GU cancers). There was a significant association between GI bleeding and new GI cancers (HR, 12.9; 95% CI, 9.77 to 17.0; *P* < .0001). There was also a significant, but much weaker, association between non-GI bleeding and new GI cancers (HR, 1.77; 95% CI, 1.20 to 2.61; *P* = .004). A highly significant association was also noted between GU bleeding and new GU cancers (HR, 83.4; 95% CI, 58.6 to 118.6; *P* < .0001). The association between non-GU bleeding and new GU cancers was not significant.

The majority of new GI (77.1%) and GU (88.7%) cancers diagnosed after bleeding occurred within 6 months of the bleed. Rivaroxaban-based treatments compared with aspirin increased GI bleeding within the first year, but not in the second or third year, and this was accompanied by an increase in the number of GI cancers diagnosed after bleeding in the first year, but not in the second or third (Table 1).

Table 1. Frequency of GI Cancer After GI Bleeding in Year 1, 2, and 3+

Year	Rivaroxaban 2.5 mg bid + ASA 100 mg od n (%)	Rivaroxaban 5 mg bid n (%)	Aspirin 100 mg bid n (%)
1	22/268 (8.2%)	18/216 (8.3%)	8/114 (7.0%)
2	6/72 (8.3%)	6/81 (7.4%)	5/58 (8.6%)
3+	1/34 (2.9%)	2/29 (6.9%)	2/29 (6.9%)

GI, gastrointestinal.

Among COMPASS patients with vascular disease on long-term antithrombotic therapy, more than 1 in 5 new diagnoses of all cancers were preceded by bleeding and more than 75% of these cancers were diagnosed within 6 months of the bleed. This suggests that GI and GU bleeding are powerful predictors GI and GU cancer diagnosis. An early increase in GI bleeding with antithrombotic treatments appears to be associated with earlier diagnosis of GI cancer.

Prof. Eikelboom suggests that physicians detecting the occurrence of GI or GU bleeding in patients receiving antithrombotic drugs should lead to expedient evaluation for cancer in the same organ. Extended follow-up of COMPASS trial participants may help to determine whether earlier diagnosis of GI cancer in patients with GI bleeding improves cancer outcomes.

Coronary CT Angiography Reduces 5-Year Risk of Myocardial Infarction

Written by **Michiel Tent**

In patients with stable chest pain, coronary computed tomographic angiography (CTA)-guided management reduced 5-year coronary heart disease (CHD) death or non-fatal myocardial infarction (MI) compared with standard care alone in the Scottish Computed Tomography of the Heart trial [SCOT-HEART trial; Newby DE et al. *N Engl J Med*. 2018]. The final clinical outcomes were presented by David E Newby, MD, PhD, University of Edinburgh, United Kingdom.

Coronary CTA improves diagnostic certainty in the assessment of patients with stable chest pain, but its effect on 5-year clinical outcomes was unknown. The SCOT-HEART trial was designed to determine the longer-term effect of CTA on investigations, treatments, and clinical outcomes. The trial had an open-label, multicentre, parallel-group design. Eligible for inclusion were patients aged 18 to 75 years with stable chest pain who had been referred by a primary care physician to an outpatient cardiology clinic. A total of 4,146 patients from 12 Scottish cardiology centres were included. Following routine clinical evaluation, they were randomly assigned to either standard care plus CTA (n = 2,073) or standard care alone (n = 2,073). Clinical endpoints included death (cardiovascular [CV] death, non-CV death, death from CHD, and death from any cause), MI, and stroke. The primary endpoint was death from CHD or nonfatal MI at 5 years.

The median duration of follow-up was 4.8 years, comprising a total of 20,254 patient-years. The rate of the primary long-term endpoint was significantly lower in the CTA group than in the standard-care group (2.3% [n = 48] vs 3.9% [n = 81]; HR, 0.59; 95% CI, 0.41 to 0.84; *P* = .004). This difference was driven primarily by a lower rate of nonfatal MI in the CTA group (HR, 0.60; 95% CI, 0.41 to 0.87). There were no significant differences in non-CV death or deaths from any cause.

The rates of invasive coronary angiography (ICA) and coronary revascularisation were higher in the CTA group than in the standard-care group in the first few months of follow-up. At 5 years however, overall rates were similar. ICA was performed in 491 patients in the CTA group and in 502 patients in the standard-care group (HR, 1.00; 95% CI, 0.88 to 1.13). Coronary revascularisation was performed in 279 patients in the CTA group and in 267 in the standard-care group (HR, 1.07; 95% CI, 0.91 to 1.27). Beyond the first year analysis, patients assigned to CTA had lower rates of ICA (HR, 0.70; 95% CI, 0.52 to 0.95), and of coronary

revascularisation (HR, 0.59; 95% CI, 0.38 to 0.90). In the CTA group, more preventive therapies were initiated (OR, 1.40; 95% CI, 1.19 to 1.65), as well as more antianginal therapies (OR, 1.27; 95% CI, 1.05 to 1.54).

Prof. Newby concluded that, in this trial, CTA in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from CHD or nonfatal MI at 5 years than standard care alone, without resulting in a significantly higher rate of coronary angiography or coronary revascularisation. Early increases in ICA and coronary revascularisation were offset by lower rates beyond 1 year. Benefits seem to be attributable to better targeted preventive therapies and coronary revascularisation.

Ticagrelor Monotherapy Beyond 1 Month No Better Than Standard Dual Antiplatelet Therapy After Stenting

Written by **Constance de Koning**

Discontinuing aspirin after 1 month continuing monotherapy with ticagrelor is no better than standard dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS) or stable coronary artery disease (CAD), according to the results of the GLOBAL LEADERS study [Vranckx P et al. *Lancet*. 2018] presented by Patrick W. Serruys, MD, PhD, Erasmus Medical Center, Rotterdam, the Netherlands.

In this multicentre, open-label, superiority trial, a total of 15,968 patients who underwent PCI with a biolimus A9-eluting stent for stable CAD or ACS were randomised to either 75-100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy (n = 7,988), or standard DAPT with 75-100 mg aspirin daily plus either 75 mg clopidogrel daily (in patients with stable CAD) or 90 mg ticagrelor twice daily (in patients with ACS) for 12 months, followed by aspirin monotherapy for 12 months (n = 7,980). The composite primary endpoint was the cumulative incidence of all-cause death or new Q-wave myocardial infarction (MI) within 2 years; the secondary endpoint was the rate of moderate or severe bleeding (BARC criteria 3 or 5) over the 2-year period.

At 12 months, all-cause mortality or new Q-wave MI was 1.95% in the ticagrelor group versus 2.47% in the standard DAPT group (risk ratio [RR], 0.79; 95% CI, 0.64 to 0.98; *P* = .028; Table 1).

Table 1. Primary and Secondary Outcomes at 12 Months (ITT)

	Experimental group	Reference group	Risk Ratio (95% CI)	*P*-value
Number of patients	n = 7,980	n = 7,988		
All-cause mortality or new Q-wave MI	1.95% (156)	2.47% (197)	0.79 (0.64-0.98)	.028
All-cause mortality	1.35% (108)	1.64% (131)	0.82 (0.64-1.06)	.138
New Q-wave MI	0.60% (48)	0.86% (69)	0.70 (0.48-1.00)	.052

ITT, intent-to-treat; MI, myocardial infarction.

At 24 months, all-cause mortality or new Q-wave MI was 3.81% for ticagrelor versus 4.37% for standard DAPT (RR, 0.87; 95% CI; 0.75 to 1.01; *P* = .073; Table 2).

Table 2. Primary and Secondary Outcomes at 24 Months (ITT)

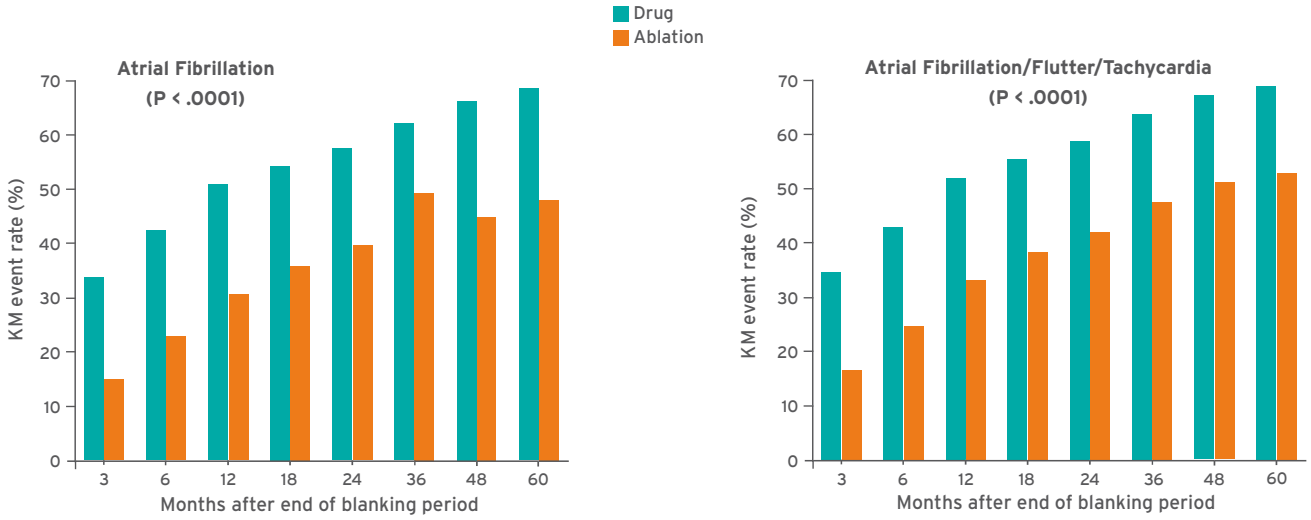
	Experimental group	Reference group	Risk Ratio (95% CI)	*P*-value
Number of patients	n = 7,980	n = 7,988		
All-cause mortality or new Q-wave MI	3.81% (304)	4.37% (349)	0.87 (0.75-1.01)	.073
All-cause mortality	2.81% (224)	3.17% (253)	0.88 (0.74-1.06)	.18
New Q-wave MI	1.04% (83)	1.29% (103)	0.80 (0.60-1.07)	.14

ITT, intent-to-treat; MI, myocardial infarction.

Major bleeding (BARC 3 or 5) was observed in 2.04% of patients who received aspirin for 1 month and extended ticagrelor and in 2.12% of patients treated with conventional DAPT (RR, 0.97; 95% CI, 0.78 to 1.20; *P* = .767).

Although the rate of serious adverse events did not differ significantly between the two groups, according to Prof. Serruys, adherence may have compromised the assessment of superiority, as in the second year of treatment 78% of ticagrelor patients were adherent versus 93% in the reference group. Investigator reporting was used without central adjudication on the secondary outcomes, so it is possible that bias or misclassification could have occurred. Additionally, the unexpected lower rate of all-cause mortality and the composite primary endpoint limits the predictive power of the study. In conclusion, ticagrelor plus low-dose aspirin for 1 month followed by 23 months of ticagrelor monotherapy was not superior in reducing the 2-year rates of all-cause mortality and non-fatal, new Q-wave MI compared with 12 months of standard DAPT followed by aspirin monotherapy in patients who underwent PCI.

Figure 1. Cumulative First Recurrence Event Rates After 90 Days of Blanking



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Ablation Reduced Recurrent Arrhythmias Compared With Drug Therapy in AF Patients

Written by **Michiel Tent**

In the CABANA trial, catheter ablation was associated with a significant relative risk reduction of around 50% in recurrence of atrial arrhythmias in patients with atrial fibrillation (AF) compared with drug therapy. AF was the dominant first recurrent rhythm after the 90-day blanking period during the 5 years of follow-up.

The results of this secondary analysis of the CABANA trial focusing on the recurrence of atrial arrhythmias were presented by Jeanne Poole, MD, University of Washington Medical Center, Seattle, Washington, USA. The single-blind CABANA trial randomised 2,204 symptomatic patients with paroxysmal or persistent AF 1:1 to percutaneous left atrial catheter ablation or medical therapy. Patients aged ≥ 65 years or < 65 years with > 1 risk factor for stroke who were eligible for both ablation and ≥ 2 rhythm or rate controlling drugs were followed for a median of 4 years [Packer DL et al. *Am Heart J*. 2018]. The primary composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest was not significantly reduced with ablation (HR, 0.86; 95% CI, 0.65 to 1.15; *P* = .30) [Packer DL. HRS 2018 Scientific Sessions].

The current analysis reported rates of recurrent atrial arrhythmias using electrocardiographic monitoring every 3 months (monitoring duration alternated between 24 hours and 96 hours each 3-month period). In CABANA, a 2-channel recording system was used for electrocardiogram monitoring by 86% of enrolling sites, while the remaining centres employed other heart rhythm monitoring systems. Endpoint-determining rhythms (EDR) were defined as: AF, atrial flutter (AFL), or atrial tachycardia (AT) lasting ≥ 30 seconds.

The hazard ratios of a first episode after 90 days of blanking in 1,240 patients with a CABANA recorder in patients randomised to AF ablation versus drug therapy were 0.52 (95% CI, 0.45 to 0.60; *P* < .001) for recurrent AF and 0.53 (95% CI, 0.46 to 0.62; *P* < .001) for the combined outcome of AF, AFL, and AT. In 803 patients without a CABANA recorder, the results similarly favoured the ablation group (HR 0.50 and 0.56, respectively). Ablation was associated with a significant reduction across the 5 years of therapy in cumulative first recurrence event rate, again after 90 days of blanking (Figure 1). There were no reductions in the rates of AFL and AT by treatment strategy (HR, 1.08; 95% CI, 0.83 to 1.39; *P* = .58); only the outcome of recurrent AF was reduced by ablation (HR, 0.53; 95% CI, 0.46 to 0.62; *P* < .001). The average AF burden as assessed by biannual 96-hour Holter monitoring was also found to be significantly lower in the ablation group across all 5 years of treatment (*P* < .0001). These findings were significant regardless of the baseline pattern of AF, paroxysmal or persistent/long-standing persistent AF.

Looking to the future, Prof. Poole noted that this large base of rhythm data provides a foundation for addressing many other important questions with respect to recurrent arrhythmias and treatment of patients with AF.

CAMELLIA-TIMI 61 Established Cardiovascular Safety of Lorcaserin

Written by **Constance de Koning**

Adding lorcaserin to diet and exercise resulted in sustained weight loss compared with placebo without increasing the risk for major adverse cardiovascular events (MACE) in the CAMELLIA-TIMI 61 study [Bohula EA et al. *N Engl J Med*. 2018], presented by Erin A. Bohula, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA.

Weight loss is an important factor when improving cardiovascular (CV) risk factors, but thus far there have been no agents with proven CV safety. In clinical trials, lorcaserin, a selective agonist of the 5HT-2C receptor, has shown efficacy for weight loss, but its CV safety had not been tested.

Twelve-thousand overweight and obese patients were included in this is multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Patients who had established CV disease or CV risk factors, such as type 2 diabetes, and a median baseline body mass index of 35 mg/kg^2 were randomised 1:1 to receive lorcaserin 10 mg twice daily or placebo. Median follow-up was 3.3 years. The primary CV efficacy endpoint was MACE+ (i.e., MACE, hospitalisation for heart failure, unstable angina, or coronary revascularisation). The primary CV safety endpoint was MACE (i.e., CV death, myocardial infarction, or cerebrovascular accident).

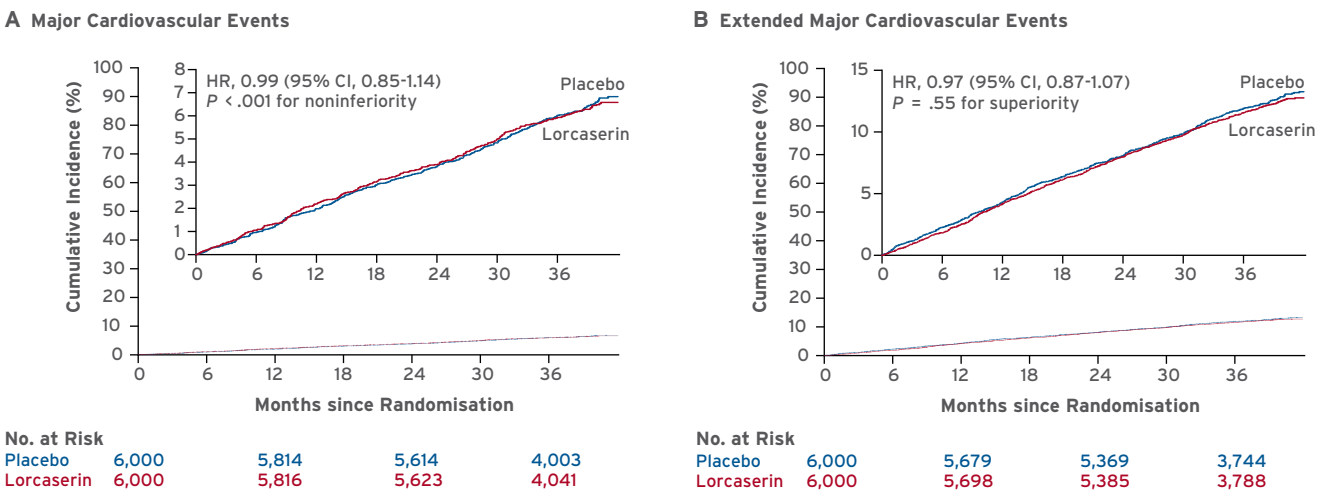
A total of 98% of patients in the lorcaserin group and 97% in the placebo group completed the study. Weight loss achieved with lorcaserin was on average 4.2 kg after 1 year versus 1.4 kg for placebo; a between group difference of 2.8 kg (P < .001). At 1 year, 38.7% of patients on lorcaserin had ≥ 5% weight loss compared with 17.4% of those on placebo (OR, 3.01; 95% CI, 2.74 to 3.30; P < .001). Ten percent weight loss or more was achieved by 14.6% and 4.8% of patients, respectively (OR, 3.40; 95% CI, 2.92 to 3.95; P < .001). Weight loss with lorcaserin was sustained over time and remained significant up to 3.3 years.

At 3.3. years, MACE occurred in 6.1% of the lorcaserin-treated patients and 6.2% of patients treated with placebo (HR, 0.99; 95% CI, 0.85 to 1.14; P < .001 for non-inferiority ; Figure 1A). The composite of MACE+ occurred in 707 patients (12.8%, or 4.1% per year) in the lorcaserin group and in 727 (13.3% or 4.2% per year) in the placebo group (HR, 0.97; 95% CI, 0.87 to 1.07; P =.55; Figure 1B).

Adverse events considered to be possibly related to the study drug lead to discontinuation in 7.2% of lorcaserin patients versus 3.7% of placebo patients. The most commonly reported adverse events leading to discontinuation in the lorcaserin group were dizziness, fatigue, headache, diarrhea, and nausea. Lorcaserin seemed to have a favourable effect on glycaemia although it was suggested this may be due to the achieved weight loss.

These findings support using lorcaserin as an adjunct to lifestyle modification for long-term weight management, even in high-risk CV patients. However, whether this new therapy is a cost-effective and sustainable approach to achieving a modest degree of weight loss without additional CV benefit compared with lifestyle changes or bariatric surgery remains to be seen.

Figure 1. Major Adverse Cardiac Outcomes



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Percutaneous Mitral Valve Repair Is Safe in Patients With Secondary Mitral Regurgitation but Does Not Improve Outcomes

Written by **Phil Vinall**

Results from the MITRA.fr study show that percutaneous mitral valve repair is as safe as optimal medical treatment (OMT) but does not reduce death or unplanned hospitalisation for heart failure (HF) in patients with secondary mitral regurgitation (MR). The data were presented by Jean-Francois Obadia, MD, PhD, Civils Hospices of Lyon, France [Obadia JF et al. *N Engl J Med*. 2018]

The MITRA.fr study was a national, multicentre, investigator-initiated, open-label, randomised trial. The objective was to evaluate the clinical efficacy and safety of percutaneous mitral valve repair using the MitraClip system plus OMT versus OMT alone in patients with severe symptomatic secondary MR contraindicated for surgical repair. Patients were randomly assigned to receive the MitraClip plus OMT (n = 152) or OMT alone (n = 152). The primary endpoint was a composite of all-cause mortality or unplanned hospitalisations for HF at 12 months after randomisation.

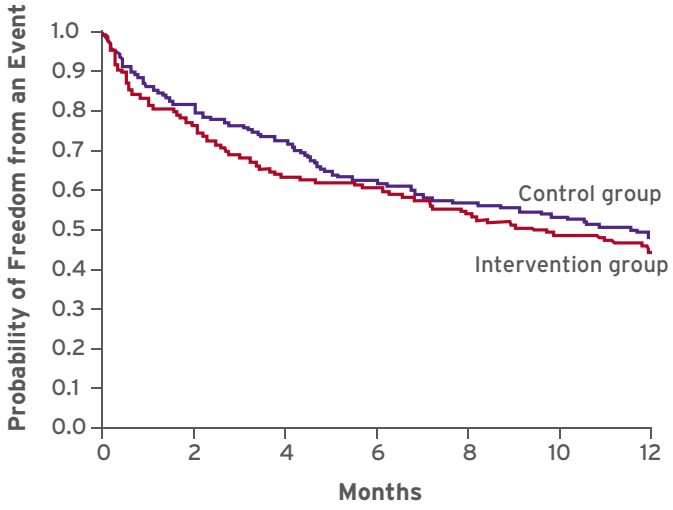
Eligibility requirements included: age > 18 years; NYHA class ≥ II; ≥ 1 hospitalisation for HF within 12 months preceding randomisation; severe secondary MR with an effective regurgitant orifice > 20 mm^2 or regurgitant volume > 30 mL/beat and left ventricular ejection fraction between 15% and 40%. Patients considered eligible for mitral surgery intervention according to the Heart Team and those having a Corelab assessment outside of the predefined parameters were excluded.

The per-protocol analysis includes 109 patients in the MitraClip group and 137 in the OMT group. Participants were a mean age of 70 years (> 75% male). Sixty percent had ischaemic cardiomyopathy and 2/3 were either NYHA Class III or IV. Mean ejection fraction was 33%; mean effective regurgitation orifice area was 31 mm^2; and mean systolic blood pressure was 108.5 mm Hg. The majority of participants were being treated with diuretics, beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and/or a mineralocorticoid receptor antagonist.

The rate of the primary outcome of all-cause death or unplanned rehospitalisation for HF did not differ significantly between the two groups (54.6% for patients who received the MitraClip plus OMT vs 51.3% for those who received OMT only). There were also no differences in the components or within the intention-to-treat or per-protocol analysis (OR, 1.16; 95% CI, 0.73 to 1.84; *P* = .53; Figure 1).

Implantation was successful in 96% of patients. The mortality rate at 1-year was similar for the two groups (24.3% and 22.4%, in the intervention and control groups, respectively). There were no periprocedural incidents of urgent conversion to heart surgery or periprocedural mortality at 3 days. Vascular complications requiring surgery or haemorrhage resulting in transfusion occurred in 3.5% of patients; 1.4% had a cardiac embolism or tamponade. MR grade improved in the

Figure 1. Primary Composite Endpoint



No. at Risk							
Control group	152	123	109	94	86	80	73
Intervention group	151	114	95	91	81	73	67

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MitraClip group at discharge and was maintained at 12 months. NYHA class improved significantly in both groups for the majority of patients (from Class II and III at baseline to Class I and II at discharge; $P < .001$).

Percutaneous correction of secondary MR with the MitraClip system is safe but does not improve patient outcomes when compared with OMT. The effectiveness of earlier intervention in a more selected sub-group of patients remains to be explored.

Rivaroxaban Does not Reduce the Composite of Death, MI or Stroke in Heart Failure Patients

Written by **Constance de Koning**

Patients with heart failure are at heightened risk of adverse cardiovascular (CV) events including thromboembolic complications such as stroke [Cleland JGF et al. *Am Heart J*. 2004; Massie BM et al. *Circulation*. 2009; Homma S et al. *N Engl J* Med. 2012; Zannad F et al. *Eur J Heart Fail*. 2015]. Low-dose rivaroxaban (2.5 mg) has been shown to reduce CV death, myocardial infarction (MI), and stroke in patients with acute coronary syndromes (ACS) and in selected high-risk patients with stable coronary artery disease (CAD) when added to antiplatelet agents, according to Faiez Zannad, MD, Université de Lorraine, Nancy, France.

It was hypothesised that the addition of rivaroxaban 2.5 mg twice daily to background antiplatelet therapy would reduce risk of major adverse CV events in patients with recent worsening of congestive heart failure (CHF) and underlying CAD compared with placebo.

The Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease trial [COMMANDER HF; Zannad F et al. *N Eng J Med*. 2018] was a randomised, double-blind, parallel-group, event-driven, multicentre study. The primary efficacy outcome was the composite of all-cause mortality, MI or stroke following a HF event. The principal safety outcome was the composite of fatal bleeding or bleeding into a critical space, which could potentially lead to permanent disability. Eligible patients (n = 5,022) were assigned to rivaroxaban 2.5 mg twice daily or placebo added to standard care. Participants had at least a 3-month history of CHF with reduced left ventricular ejection fraction ≤ 40%, CAD, and elevated plasma BNP or NT-proBNP during the index event. Exclusion criteria were a high risk of bleeding, atrial fibrillation (AF), or another condition that required long-term anticoagulation.

The primary endpoint was not significantly different between groups and occurred in 13.4% of rivaroxaban patients and in 14.3% of placebo patients (HR, 0.94; 95% CI, 0.84 to 1.05; $P = .27$). There was also no difference in all-cause mortality between the groups (11.4% and 11.6%, respectively; HR, 0.98; 95% CI, 0.87 to 1.10). There was a nominally significant reduction in stroke with rivaroxaban compared with placebo (1.08% vs 1.62%: HR, 0.66; 95% CI, 0.47 to 0.95) and a trend for MI (HR, 0.83; 95% CI, 0.63 to 1.08). The principal safety outcome occurred in 0.7% of rivaroxaban patients and 0.9% of placebo patients (HR, 0.80; 95% CI, 0.43 to 1.49; $P = .48$).

Low-dose rivaroxaban as an addition to guideline-based treatment does not improve the composite of all-cause mortality, MI, or stroke in patients with recent worsening of CHF and reduced ejection fraction, and CAD without AF. Prof. Zannad noted that as this study included HF patients who were at high risk after recent HF hospitalisation, it opened the possibility that HF deaths made up a substantial proportion of all deaths in this population instead of deaths due to atherothrombotic events. Trends for reduction in MI and stroke support the hypothesis that more potent antithrombotic strategies may reduce thrombotic risk in patients with HF. However, rates of death are high and may occur from predominantly non-thrombotic causes attenuating benefit for the primary composite endpoint of this trial. Future studies focused on outcomes modifiable with antithrombotic therapies may demonstrate efficacy.

FRANCE-TAVI Registry Results

Written by **Michiel Tent**

Male gender, renal failure, and atrial fibrillation (AF) predicted mortality at 3 years of follow-up in patients who underwent successful transcatheter aortic valve replacement (TAVR). Primarily for AF, anticoagulation was associated with a lower risk of bioprosthetic valve dysfunction (BVD) after TAVR but a higher risk of long-term mortality.

The results from FRANCE-TAVI, a prospective, multicentre, nation-wide French registry were, presented by Jean-Philippe Collet, MD, Sorbonne University and Pitie Salpetriere Hospital, Paris, France [Overtchouk P et al. *J Am Coll Cardiol*. 2018]. Prof. Collet explained that the optimal antithrombotic treatment after TAVR is still unknown. Dual antiplatelet therapy (DAPT) is used most frequently but single antiplatelet therapy or oral anticoagulation (OAC) are also used. The objectives of the French research group were two-fold: to investigate whether antithrombotic treatment influences long-term mortality and early BVD, and to explore independent correlates of long-term mortality and early BVD after TAVR. BVD was defined as increased prosthetic gradient ≥ 10 mm Hg or new gradient ≥ 20 mm Hg, and was identified by multislice computed tomography (MSCT).

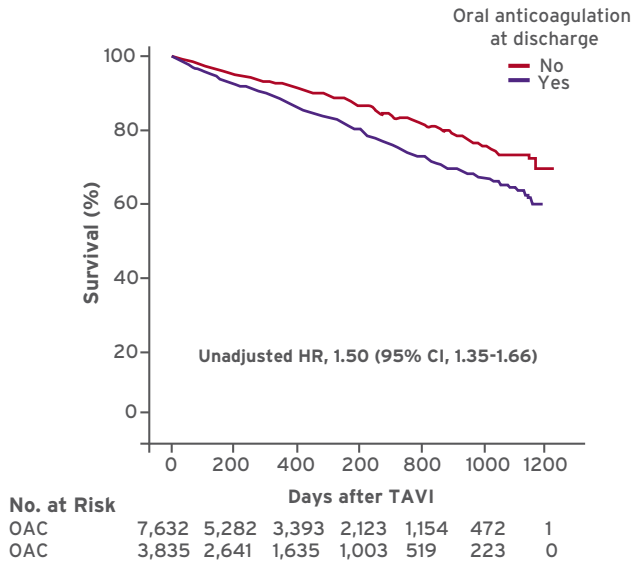
Between 1 January 2013 and 31 December 2015, 12,804 patients were included. Of these, 11,469 were alive at discharge with known antithrombotic treatment and were analysed for mortality. Mean age was 82.8 years, mean logistic Euroscore was 17.8, and mean follow-up was 495 days. A total of 2,555 patients had at least two echocardiographic evaluations and were eligible for BVD assessment. The prevalence of BVD post-TAVR in the registry was 5.5% (n = 140). One third of patients had a history of AF; the same proportion had OAC at discharge (n = 3,836), primarily for the prevention of cardioembolic stroke. The results showed that neither aspirin nor clopidogrel were independently associated with mortality (Table 1).

Table 1. Independent Correlates of Mortality

	Adjusted HR (95% CI)	*P*-value
Male gender	1.63 (1.44-1.84)	.001
History of AF	1.41 (1.23-1.62)	.001
Chronic renal failure	1.37 (1.23-1.53)	.001

Prof. Collet noted that anticoagulation at discharge remained a correlate of mortality (unadjusted HR, 1.50; 95% CI, 1.35 to 1.66; Figure 1) independent of AF, despite the strong correlation between AF and mortality.

Figure 1. Kaplan-Meier Survival Curves According to Anticoagulation at Discharge



OAC, oral anticoagulation.

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Anticoagulation at discharge was also independently associated with lower rates of BVD (adjusted OR, 0.54; 95% CI, 0.35 to 0.82; *P* = .005). The same was true for a non-femoral approach (adjusted OR, 0.53; 95% CI, 0.28 to 1.02; *P* = .049). A higher risk of BVD was yielded by chronic renal failure (adjusted OR, 1.46; 95% CI, 1.03 to 2.08; *P* = .034); and by a prosthesis size of ≤ 23 mm (adjusted OR, 3.43; 95% CI, 2.41 to 4.89; *P* < .001). Prof. Collet noted that antithrombotic treatment is driven not by the procedure but by patient characteristics. Of the patients in this study, 70% used OAC therapy to manage their AF and use of OAC was associated with lower risk of BVD.

Limitations of the study include its non-randomised, observational nature, which means unknown confounders cannot be excluded; the declarative clinical outcome reporting; treatment cross-over, which could not be assessed; and the identification of BVD with MSCT, which may have led to different correlates.

Primary Results From the MARINER Trial

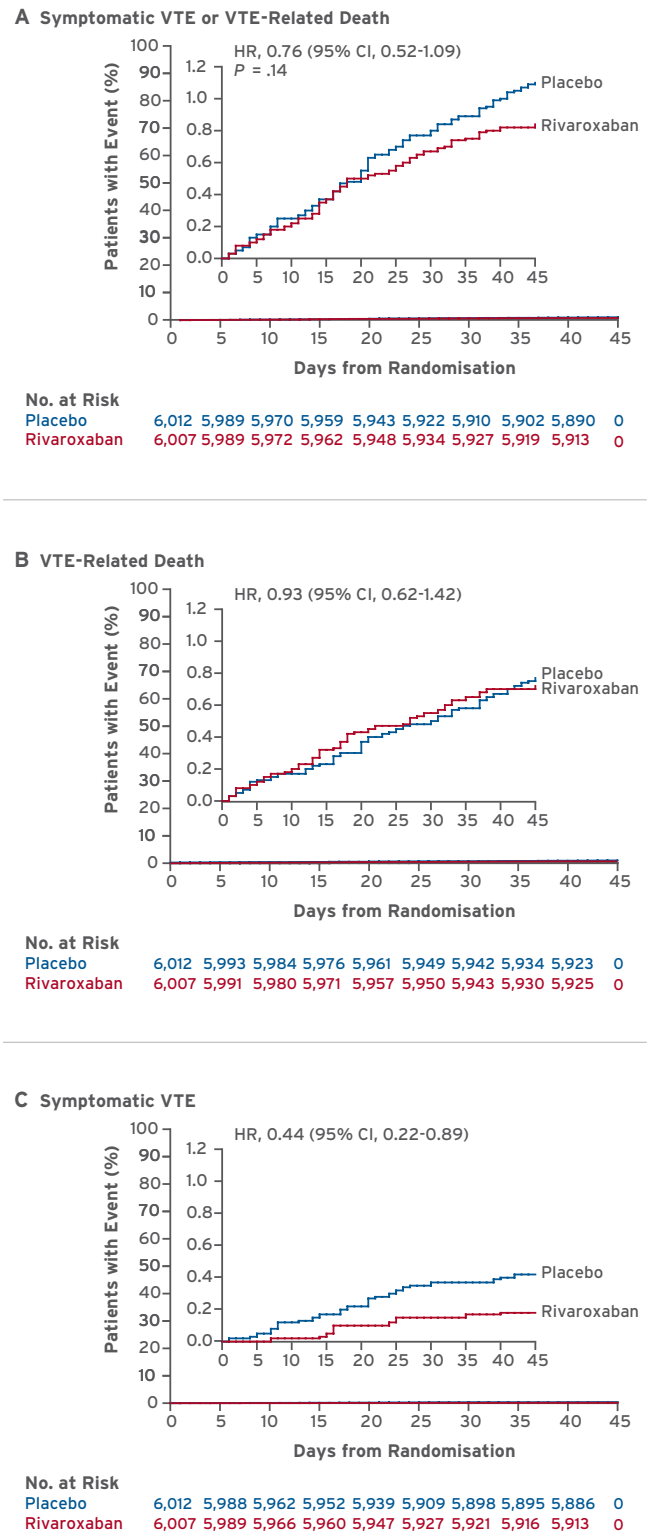
Written by **Constance de Koning**

Primary results from the MARINER trial [Spyropoulos AC et al. *N Engl J Med*. 2018] showed that treatment with rivaroxaban did not significantly reduce the risk of symptomatic venous thromboembolism (VTE) and VTE-related death in medically ill patients after hospital discharge.

Hospitalised patients run a substantial risk of developing VTE after discharge. According to Alex C. Spyropoulos, MD, Lennox Hill Hospital, New York, USA, the role of extended thromboprophylaxis has been investigated but has either shown excess bleeding or beneficial effects from reducing mostly asymptomatic deep vein thrombosis (DVT). MARINER was designed to compare rivaroxaban with placebo for the prevention of symptomatic VTE and VTE-related death in medically ill patients at heightened risk of VTE after discharge from the hospital. The principal safety objective was major bleeding.

The trial was a randomised, double-blind, placebo-controlled, event-driven study that included a total of 12,024 patients aged ≥ 40 years who had been hospitalised with an acute medical illness for 3-10 consecutive days and had an elevated VTE risk, defined as a modified IMPROVE score ≥ 4 or a score of 2 or 3 plus a plasma D-dimer level more than twice the upper limit of normal. The rivaroxaban regimen consisted of 10 mg once daily or 7.5 mg for patients with a creatinine clearance of 30 to < 50 ml/min. The first dose was given on the day of discharge and the last dose at Day 45. Patients were followed up for an additional 30 days. Baseline characteristics were similar between groups.

Figure 1. Primary Efficacy Outcome up to Day 45



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The results showed that symptomatic VTE and VTE-related death up to Day 45 occurred in 66 patients receiving placebo versus 50 patients receiving rivaroxaban. This represented a 24% relative risk reduction or a 0.27% absolute risk reduction (HR, 0.76; 95% CI, 0.52 to 1.09; *P* = .136 ; Figure 1A).

There was a slight benefit in the patients who received the full 10 mg rivaroxaban dose (0.65% vs 0.98%; *P* = .075), with no such signal in the patients with moderate renal insufficiency who received the lower 7.5 mg dose. Exploratory, prespecified secondary outcomes showed a nominally significant 56% reduction in symptomatic VTE (*P* = .023) and a 27% reduction in the composite of symptomatic VTE and all-cause mortality (*P* = .033) with rivaroxaban. Major bleeding was low in both groups (0.28% for rivaroxaban and 0.15% for placebo; HR, 1.88; 95% CI, 0.84 to 4.23; *P* = .124).

Rivaroxaban in this trial did not significantly reduce the composite of symptomatic VTE and VTE-related death in at-risk patients post-discharge (Figure 1B). The number of major bleeding events with rivaroxaban was low, with no significant increase in major, critical or fatal bleeding. These differences in risk suggest that the number needed-to-treat (NTT) to prevent one symptomatic VTE is 430 while the NTT to cause one major bleed is 856.

The event rate for the primary endpoint in the population selected was low (1.1% over 45 days in the placebo group) relative to that estimated in the design (2.5%) and even lower for the endpoint of symptomatic VTE (0.42%, 25 of 6,012 randomised to placebo). The trial was powered estimating a 40% relative risk reduction requiring 161 primary endpoint events. However, the observed relative risk reduction was 24% with only 116 events, raising the question of whether the trial was adequately powered. That no effect was observed with rivaroxaban on VTE-related death raises the question whether the definition used in the trial, which included sudden and unexplained death, was specific enough to capture true thrombotic related causes of death.

It should be noted that the observed event rate in the placebo group was 1.1% – less than half the estimate in the original protocol (2.5%). Although a protocol amendment increased the enrolment from 8,000 to 12,000 patients to allow more primary endpoint events to accrue, the final number was fewer than anticipated (116 vs 161 events). These results indicate that either a higher risk population and/or larger trial with a greater number of events would be needed to determine whether low-dose oral anticoagulation may significantly reduce recurrent VTE events in medically ill patients.

Primary Prevention With Aspirin: Effective in Patients with Diabetes, but Role in Moderate-Risk Patients Less Clear

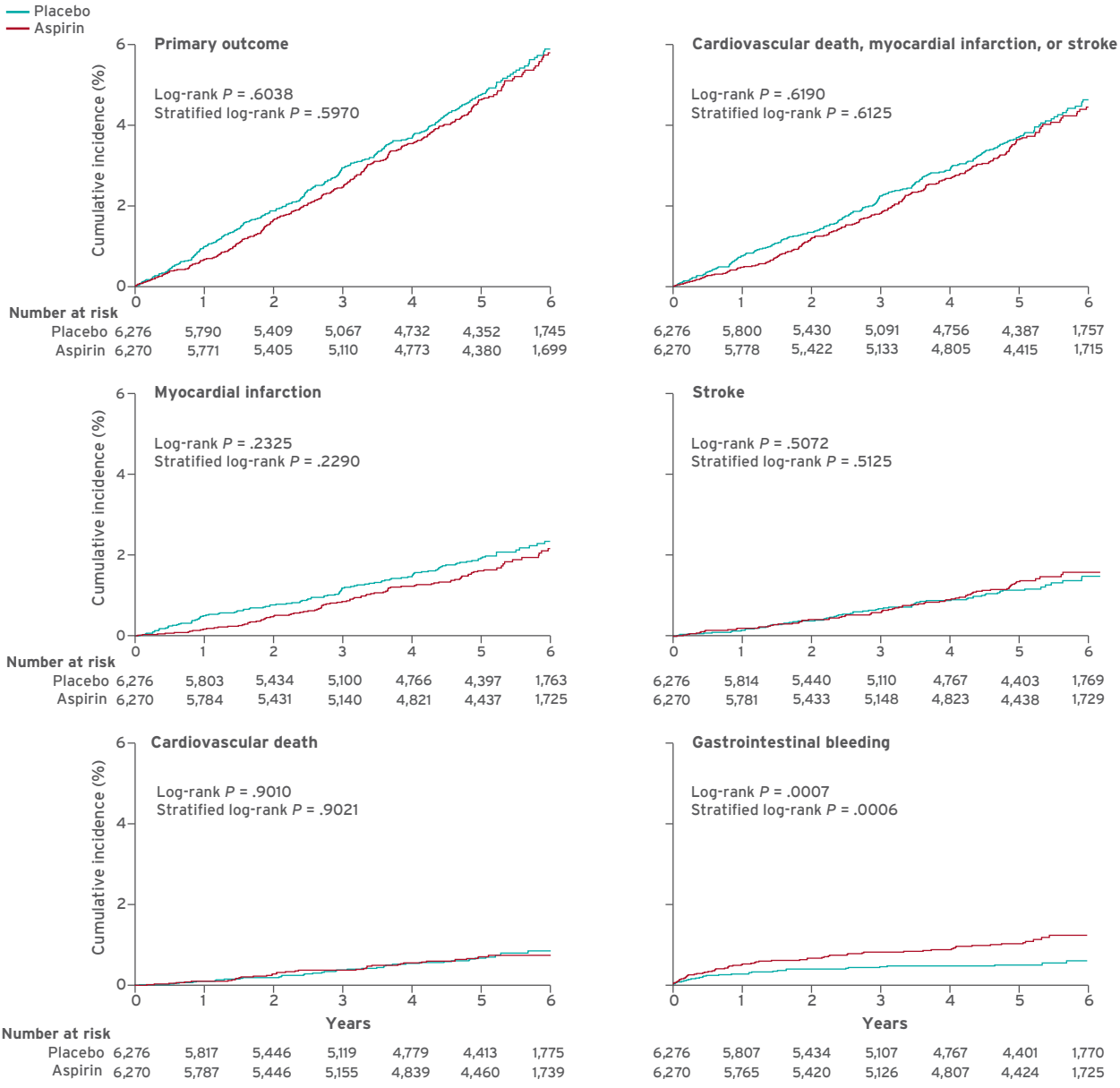
Written by **Constance de Koning**

Prevention of cardiovascular (CV) events plays a key role in achieving optimal patient outcomes, especially in high-risk groups. Although aspirin did not reduce CV risk in moderate-risk patients, it did prevent serious vascular events (SVE) in diabetic patients without CV disease (CVD), although major bleeding was increased.

No Clear Role for Aspirin in CV Risk Reduction in Moderate-Risk Patients

Findings from the Aspirin to Reduce Risk of Initial Vascular Events trial [ARRIVE; Gaziano JM et al. *Lancet*. 2018] showed that aspirin does not reduce the long-term risk of CV events in patients at moderate risk. This randomised, double-blind, placebo-controlled, multicentre trial assessed the efficacy and safety of aspirin in patients at moderate estimated risk of a CV event (men age ≥ 55 years with ≥ 2 CV risk factors and women age ≥ 60 years with ≥ 3 CV risk factors). Patients had no known history of CVD or diabetes plus an estimated 10-year risk of major coronary heart

Figure 1. Key outcomes



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disease events of 10-20% corresponding to a 10-year 20-30% CVD risk were randomised to 100 mg enteric-coated aspirin daily (n = 6,270) or placebo (n = 6,276). Statins were used by 43% of patients in this study. The primary efficacy endpoint was time of first occurrence of composite endpoint (CVD death, myocardial infarction [MI], stroke, unstable angina, transient ischaemic attack [TIA]). Researchers found that 4.3% of patients taking aspirin and 4.5% of patients taking placebo experienced the primary endpoint over a mean of 5 years (HR, 0.96; 95% CI, 0.81 to 1.13; *P* = .60). The primary safety endpoints were haemorrhagic events and incidence of other adverse events; gastrointestinal bleeding (GI) events occurred in 0.97% of patients taking aspirin and in 0.46% of patients on placebo (HR, 2.11; 95% CI, 1.36 to 3.28; *P* = .0007). Rates of severe GI bleeding were extremely low (0.06% for aspirin and 0.03% for placebo) The mortality rates were 2.55% in the aspirin group and 2.57% in the placebo group (HR, 0.99; 95% CI, 0.80 to 1.24; *P* = .95). Other findings included a lower risk of fatal or non-fatal MI for patients on aspirin if they were at least 60% compliant with treatment: 1.52% versus 1.78% in the placebo group (HR, 0.85; 95% CI, 0.64 to 1.11; *P* = 0.23; Figure 1) but not reduction in stroke (1.2% vs 1.07%; HR, 1.12; 95% CI, 0.80 to 1.55; *P* = .507).

J. Michael Gaziano, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, added that despite a lack of overall reduction in CV events, these results emphasised the ability of aspirin to reduce the risk of a first non-fatal MI without affecting the risk of total stroke, while providing more insights into the efficacy and safety of aspirin in the primary prevention of CVD in older individuals and women.

Aspirin Prevented SVE in Diabetic Patients Without CVD but Caused Major Bleeding

The risks and benefits of aspirin to prevent a first CV event in patients with diabetes was evaluated in the Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus trial [ASCEND; ASCEND Study Collaborative Group. *N Engl J Med*. 2018]. A total of 15,480 patients with diabetes (94% type 2, median duration 7 years) and no prior CVD were randomised to aspirin 100 mg daily or placebo, with a mean follow-up of 7.4 years. The primary efficacy outcome was the first SVE (i.e., MI, stroke or TIA, or vascular death, excluding any confirmed intracranial haemorrhage). The primary safety outcome was the first major bleeding event. Secondary outcomes included GI cancer. Statins were used by approximately 75% of participants. Aspirin significantly reduced the risk of a SVE (non-fatal MI, stroke or TIA, or vascular death; 8.5% vs 9.6%; rate ratio, 0.88; 95% CI, 0.79 to 0.97; *P* = .01). A breakdown of the outcomes per separate SVE is shown in Table 1.

Table 1. Components of Primary Efficacy Outcome Plus Revascularisation

Type of event	Aspirin (n = 7,740)	Placebo (n = 7,740)
	no. of participants with events (%)	
Any SVE	658 (8.5)	743 (9.6)
Any arterial revascularisation	340 (4.4)	384 (5.0)
Any SVE or revascularisation	833 (10.8)	936 (12.1)

SVE, serious vascular event.

However, these outcomes came with an increased risk of major bleeding (4.1% vs 3.2%; HR, 1.29; 95% CI, 1.09 to 1.52; *P* = .003), of which 41% were GI, 21% were sight-threatening events, 17% were intracerebral haemorrhage (ICH), and 20% were bleeding events at other sites. No significant effect of the use of aspirin on mortality from all vascular causes combined (representing ~30% of all deaths) was observed when compared with placebo. There were no between-group differences in the rates for any type of cancer after more than 7 years (11.6% in the aspirin group vs 11.5% in the placebo group; RR, 1.01; 95% CI, 0.92 to 1.11), but longer-term follow-up is ongoing.

These trials of aspirin for primary prevention suggest that aspirin may be of benefit in high-risk, compliant patients, although GI bleeding is increased.

Tafamidis Safe and Effective for Patients With Transthyretin Amyloidosis

Written by **Phil Vinall**

Transthyretin amyloidosis (ATTR) is an underdiagnosed life-threatening disease that causes restrictive cardiomyopathy (CM) and progressive heart failure. Median survival is 2.5 to 3.6 years after diagnosis and the only treatment currently available is supportive care. Tafamidis is a novel non-NSAID benzoxazole derivative that binds to the thyroxine-binding sites of both variant and wild-type transthyretin (TTR). It then inhibits dissociation of tetramers into monomers, the rate limiting step in the formation of TTR amyloid leading to CM.

Claudio Rapezzi, MD, University of Bologna, Italy, presented the results of the Transthyretin Amyloid Cardiomyopathy Clinical Trial [ATTR-ACT], a multicentre, international, double-blind, placebo-controlled, Phase 3 trial [Maurer MS et al. *Circ Heart Fail*. 2017; Maurer MS et al. *N Engl J Med*. 2018].

The primary objective of ATTR-ACT was to compare the efficacy, safety, and tolerability of 80 or 20 mg tafamidis meglumine oral daily dose with placebo plus standard of care in patients with hereditary or wild-type

ATTR-CM. After screening, patients (n = 441) were randomly assigned (2:1:2) to tafamidis 80 mg, tafamidis 20 mg, or placebo for the 30-month treatment phase. Patients were stratified for genotype (wild-type or variant) and disease severity (NYHA class).

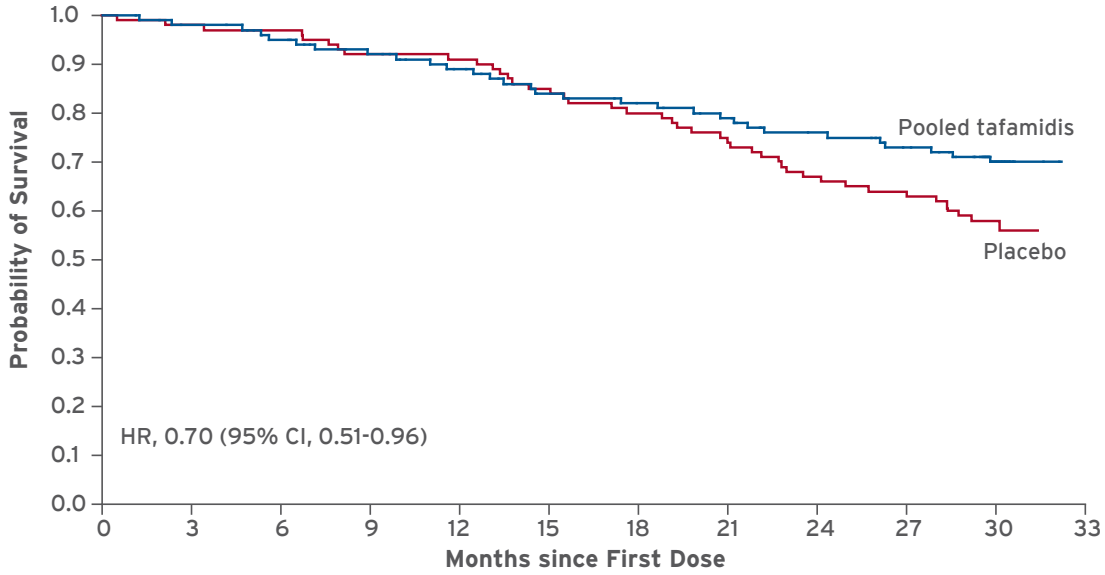
The primary efficacy analysis was the hierarchical combination of all-cause mortality and frequency of cardiovascular (CV)-related hospitalisations. Secondary endpoints included change in the 6-minute walk test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall

Figure 1. Primary Analysis and Components

A Primary Analysis, with Finkelstein-Schoenfeld Method

	No. of Patients	*P* Value from Finkelstein-Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Month 30 *no. (%)*	Average Cardiovascular-Related Hospitalisations during 30 Months among Those Alive at Month 30 *per patient per year*
Pooled Tafamidis	264			186 (70.5)	0.30
		< .001	1.70 (1.26-2.29)		
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalisations

	No. of Patients	No. of Patients with Cardiovascular-Related Hospitalisations *total no. (%)*	Cardiovascular-Related Hospitalisations *no. per yr*	Pooled Tafamidis vs Placebo Treatment Difference *relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	
				0.68 (0.56-0.81)
Placebo	177	107 (60.5)	0.70	

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Summary (KCCQ-OS) score. Data were pooled from the two tafamidis treatment groups.

Patients were a mean age of 74 years (90% male; about 80% white); 76% had the wild-type genotype. Disease severity was mostly NYHA class II and III. N-terminal pro b-type natriuretic peptide (NT-proBNP) were ~3,000. In the primary analysis, the combined endpoint of all-cause mortality and rates of CV-related hospitalisations were less frequent among the 264 patients who received tafamidis than among the 177 patients who received placebo (Win Ratio, 1.70; 95% CI, 1.26 to 2.29; $P < .001$; Figure 1A). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs 76 of 177 [42.9%]; HR, 0.70; 95% CI, 0.51 to 0.96; Figure 1B) and a lower rate of CV-related hospitalisations, with a relative risk ratio of 0.68 (0.48 per year vs 0.70 per year; 95% CI, 0.56 to 0.81; Figure 1C). At Month 30, tafamidis was also associated with a lower rate of decline in distance for the 6MWT ($P < .001$) and a lower rate of decline in KCCQ-OS score ($P < .001$). Using the more traditional Cox model, the reduction in the risk of all-cause mortality with tafamidis compared with placebo was 30% ($P = .0259$) with divergence of the event curves noted at 18 months of treatment.

Across prespecified subgroups including etiology wild-type (ATTR vs hereditary ATTR), NYHA class (I/II vs III), and tafamidis dose (80 vs 20 mg), the reduction in all-cause mortality and frequency of CV-related hospitalisations favoured tafamidis over placebo, except for patients in NYHA class III at baseline in whom CV-related hospitalisations were higher in tafamidis-treated patients, which may be a consequence of longer survival during a more severe period of disease.

Tafamidis was well tolerated with a safety profile comparable to placebo. In particular, permanent discontinuation due to adverse events, dose reductions, diarrhoea, and urinary tract infections were less common with tafamidis than with placebo.

These findings provide strong evidence that tafamidis is an effective therapy for patients with ATTR-CM and underscore the importance of early diagnosis and treatment in this disease.

Lowering the Threshold for Diagnosing MI Does Not Improve Patient Outcomes

Written by **Phil Vinall**

Improvements in assay sensitivity have allowed for highly precise quantification of very low levels of troponin, a critical factor when diagnosing myocardial infarction (MI). The 4th Universal Definition of MI now recommends use of high-sensitivity cardiac troponin (hs-cTnI) and a sex-specific 99th centile upper reference limit as the diagnostic threshold. Nicholas L. Mills, MD, PhD, Edinburgh University, United Kingdom, presented the results from the High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome trial showing that such strict classification does not improve outcomes [High-STEACS; Shah ASV et al. *Lancet*. 2018].

High-STEACS was a stepped-wedge, cluster-randomised, controlled trial designed to test the hypothesis that the new definition would reduce subsequent MI or cardiovascular (CV) death at one year in patients who had been hospitalised with suspected acute coronary syndrome.

Both the contemporary and high-sensitivity assays were measured in all patients throughout the trial. During the 6 to 12-month validation portion of the trial, care was guided by the contemporary assay and the results of the high-sensitivity assay were suppressed. After validation, sites were randomised to either early or late implementation during which time the high-sensitivity assay was used to guide care and the results of the contemporary testing was suppressed. Using the assay results, patients likely to benefit from high-sensitivity troponin were stratified into 3 groups: those without myocardial injury (hs-cTnI concentrations within the reference range); those with myocardial injury that had already been identified for some time by the contemporary assay (any cTnI concentration greater the diagnostic threshold of this assay); and patients reclassified by the high-sensitivity cardiac troponin assay (increased hs-cTnI concentration, > 16 ng/L for women, > 34 ng/L for men, cTnI concentrations below the diagnostic threshold on the contemporary assay). The primary endpoint was a composite of MI or CV death at one year.

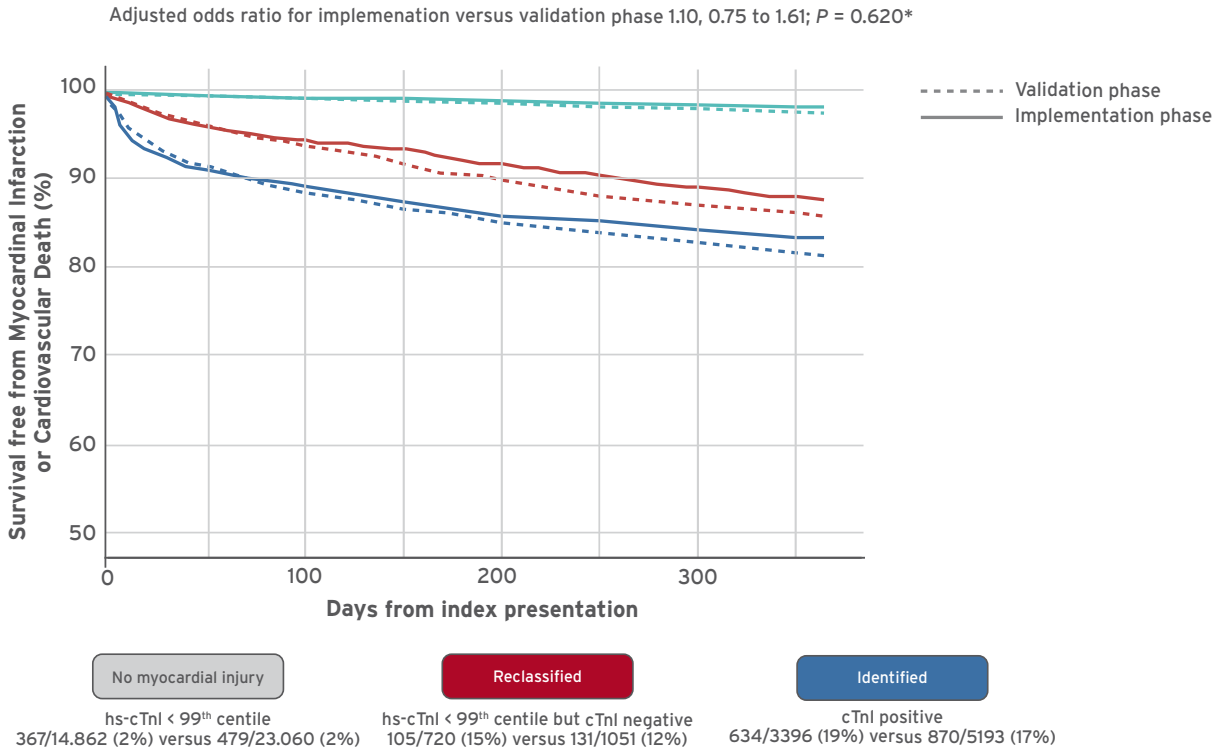
In all, 48,282 consecutive patients were enrolled (mean age 61 years; 47% female) of whom 10,360 had myocardial injury (8,589 identified by contemporary assay and 1,771 reclassified by high sensitivity assay). Patients with myocardial injury were similar except that reclassified patients were older (mean age 75 years) and more likely to be female (83%).

The primary outcome of MI or death from CV causes occurred in 2,586 patients. Patients with no myocardial injury had excellent outcomes with only 2% experiencing the primary outcome in both phases of the trial. Patients identified by contemporary assay had worse outcomes with 19% experiencing an event in the validation phase and 17% in the implementation phase. Reclassified patients, those with evidence of injury not disclosed by contemporary assay, had intermediate outcomes that did not improve with the implementation of

high sensitivity assay (15% of patients in the validation phase and 12% in the implementation phase; Figure 1).

Implementation of hs-cTnI and the 99th percentile threshold reclassified 1 in 6 patients, but only one-third had a diagnosis of type 1 MI, and the rate of subsequent MI or CV death at one year was unaffected. The results of this trial led Prof. Mills to question the recommendations by the Global Task Force for the Universal Definition of MI to base the diagnostic threshold for MI on the 99th percentile from a normal reference population.

Figure 1. Probability of Freedom From Recurrent Acute Coronary Syndrome



* linear mixed effects model adjusted for patients covariates, site, season, and time

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Dual Antithrombotic Therapy Safer and as Efficacious as Triple Therapy in AF patients Undergoing PCI

Written by **Michiel Tent**

In patients with atrial fibrillation (AF) and presenting with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI), presenters agreed that dual antithrombotic therapy (DAT: oral anticoagulant + clopidogrel) is equally effective as, and safer than triple antithrombotic therapy (TAT: oral anticoagulant [OAC] + dual antiplatelet therapy).

Kurt Huber, MD, Sigmund Freud University Medical School, Vienna, Austria, provided an update on the use of DAT and TAT for AF patients undergoing PCI. He argued that choosing DAT or TAT should be done on an individual basis. Positive outcome studies have shown safety benefits for DAT in patients with AF and PCI in cases of increased bleeding risk [Hansen ML et al. *Arch Intern Med*. 2010; Dewilde WJ et al. *Lancet*. 2013].

The current European Society of Cardiology guidelines [Valgimigli M et al. *Eur Heart J*. 2018] state that in patients with ACS treated with coronary stent implantation, dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months (class I, level A), unless there are contraindications such as excessive risk of bleeding (e.g., PRECISE-DAPT score ≥ 25). In patients with an indication for oral anticoagulation undergoing PCI, TAT should be considered for 1, 3, or 6 months (class IIa, level B) followed by up to 6 months of DAT (class IIa, level A) if concerns about ischaemic risks are prevailing. If concerns for bleeding risk are prevailing, TAT may be considered for 1 month (class IIa, level B), followed by DAT for up to 12 months (class IIa, level A); and if bleeding risk is very elevated, up to 12 months of DAT may be appropriate, in the form of clopidogrel and a non-vitamin K antagonist oral anticoagulant (NOAC; class IIa, level A).

Prof. Huber argued that drug-eluting stents (DES) with a low stent thrombosis rate may make the choice for DAT or for the duration of TAT easier. The Biofreedom™ drug-coated stent almost halved the risk of clinically driven target lesion revascularisation at 2 years compared with a bare-metal stent (BMS; HR, 0.54; 95% CI, 0.41 to 0.72; $P < .0001$) [Garot P et al. *J Am Coll Cardiol*. 2017]. The Synergy™ DES also significantly lowered the incidence of major adverse cardiac and cerebrovascular events at 1 year (12% in the DES group vs 16% in the BMS group; RR, 0.71; 95% CI, 0.52 to 0.94; $P = .02$) [Varenne O et al. *Lancet*. 2018].

Observational Trials of AF in ACS or Stenting

Andrea Rubboli, MD, Cardiology Division, Ospedale Maggiore, Bologna, Italy, discussed lessons from observational studies of AF in ACS or stenting. These studies show a high variability in the choice of antithrombotic therapy; an increased risk of bleeding with newer $P2Y_{12}$ inhibitors in TAT; and an efficacy of DAT at least equal to TAT, with a superior safety profile.

Over 170,000 patients were included in observational studies. According to Prof. Rubboli the results are difficult to compare and analyse because of overall differences in design and other aspects. There is a high variability in use of antithrombotic regimens, which is largely irrespective of the patient's risk profile: TAT ranged from 8.5 to 85%; DAT from 5 to 81%; and DAPT from 10 to 22%.

Temporal trends in Italy (2001 to 2014) in non-ST elevation (NSTE) ACS patients show a significant and progressive decrease in the use of single therapy with either antiplatelets or oral anticoagulants [De Luca L et al. *Int J Cardiol*. 2017]. The use of DAPT and of DAT was stable, while the use of TAT increased. Compared with clopidogrel, the newer $P2Y_{12}$ inhibitor prasugrel as part of TAT more than doubled the bleeding risk in NSTEMI/STEMI patients undergoing PCI (adjusted incidence rate ratio, 2.37; 95% CI, 1.36 to 4.15; $P = .003$) [Jackson LR 2nd et al. *JACC Cardiovasc Interv*. 2015]. However, the same may not be true for DAT. In registration trials of AF patients, the absolute incidence rate of major bleeding averages 4-5% for up to 12 months of TAT, which favourably compares with approximately 3.5% observed for OAC monotherapy in registration trials of non-vitamin K antagonist OACs in AF patients.

Observational studies also suggest DAT to be at least as effective as TAT, with a superior safety profile. According to Prof. Rubboli, there is no room for DAPT, except in AF patients undergoing PCI with a CHA_2DS_2-VASC score of 1, in whom adding an OAC does not decrease stroke risk, while increasing the bleeding risk, as opposed to patients with a score of ≥ 2.

Additional variables can play a role in establishing a reduced risk of bleeding, notably a high quality of OAC (reflected by being a long time in therapeutic range) when vitamin K antagonists (VKAs) are used in TAT; and use of chronic anticoagulation at the time of PCI; while a shorter (> 1 month) duration of TAT does not worsen net clinical outcomes and thus may be optimal.

TAT Versus DAT in Clinical Trials

Jean-Philippe Collet, MD, PhD, Pitié-Salpêtrière Hospital, Paris, France, weighed the benefits of triple versus dual therapy in major clinical trials in AF with ACS or stenting. He concluded that DAT is safer than TAT; patients who use TAT have a high risk of bleeding; and the most appropriate combination for DAT remains unknown.

In the open-label WOEST trial, DAT (with a VKA + clopidogrel) was associated with significantly lower rates of bleeding (19.4% vs 44.4%; HR, 0.36; 95% CI, 0.26 to 0.50; $P < .0001$) and overall mortality than TAT (VKA + clopidogrel + ASA), with similar rates of thrombotic events [Dewilde WJ. *Lancet*. 2013]. There were 573 participants, 69% of whom had AF. First generation DES and a femoral approach were the most common procedural aspects, and left main disease was an exclusion criterion. Ischaemic and bleeding risk should be weighed when choosing the duration of antiplatelet therapy, as there were significantly fewer BARC type 2 – 5 bleedings in DAT versus TAT (HR, 0.68; 95% CI, 0.47 to 0.98) in the landmark analysis at Week 6.

In the PIONEER AF-PCI trial [Gibson CM et al. *N Engl J Med*. 2016] 2,124 AF patients undergoing PCI with stent placement were randomised to one of three groups after PCI: Group 1: DAT, comprised of low-dose rivaroxaban (15 mg once dialy) plus a $P2Y_{12}$ inhibitor for 12 months; Group 2: very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months; Group 3: standard TAT therapy with a VKA (INR 2.0 to 3.0) plus DAPT for 1, 6, or 12 months. DAPT duration was prespecified and no power calculation was made. The rates of clinically significant bleeding were lower in the groups who received rivaroxaban than in the group who received standard TAT therapy with VKA + DAPT (6.8% in Group 1, 18.0% in Group 2, and 26.7% in Group 3; HR for Group 1 vs Group 3, 0.59; 95% CI, 0.47 to 0.76; $P < .001$; HR for Group 2 vs Group 3, 0.63; 95% CI, 0.50 to 0.80; $P < .001$; Figure 1). The three groups had similar efficacy rates.

In the REDUAL-PCI multicentre trial [Cannon CP et al. *N Engl J Med*. 2017], 2,725 AF patients who had undergone PCI were randomly assigned to TAT with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) plus aspirin (for 1 to 3 months; triple-therapy group), or DAT with dabigatran (110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups). The risk of bleeding was lower among those who received DAT (HR, 0.52; 95% CI, 0.42 to 0.63; $P < .001$ for noninferiority; $P < .001$ for superiority for 110 mg dabigatran; HR, 0.72; 95% CI, 0.58 to 0.88; $P < .001$ for noninferiority for 150 mg dabigatran) than among those who received TAT. DAT was noninferior to TAT with respect to the risk of thromboembolic events.

The most favourable duration of DAPT has yet to be determined, and is the subject of ongoing trials, such as the AUGUSTUS trial. The new ESC/EACTS Guidelines on Myocardial Revascularization [Neumann FJ et al. *Eur Heart J*. 2018.] present a list of strategies to avoid bleeding complications in patients with oral anticoagulants (Table 1), as well as a practical table with information on high-risk features for ischaemic events.

Table 1. Strategies to Avoid Bleeding Complications of OAC in Myocardial Revascularisation Patients

Assess ischaemic and bleeding risks using **validated risk predictors** (e.g., CHA_2DS_2-VASC, ABC, and HAS-BLED) with a focus on modifiable risk factors.
Keep **triple therapy duration as a short as possible**; dual therapy after PCI (OAC and clopidogrel) to be considered instead of triple therapy.
One should consider the **use of a NOAC instead of a VKA** when NOACs are not contraindicated.
Consider a **target INR in the lower part of the recommended target** range and maximise time in the therapeutic range (i.e., > 65%) when a VKA is used.
Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
Use **low-dose (≤ 100 mg daily) aspirin**.
Routine use of **PPIs**.

Reprinted from Neumann F-J et al. 2018 ESC/EACTS Guidelines on Myocardial Revascularization. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy394. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Innovative Strategies for Secondary Prevention

Written by **Constance de Koning**

Secondary cardiovascular (CV) prevention remains a highly dynamic field, in which new strategies are continuously being developed and tested in contemporary trials. Novel approaches include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition, anti-cytokine therapy, $P2Y_{12}$ inhibition, and targeting residual inflammatory, lipid, and thrombotic risk.

Residual Inflammatory, Lipid, and Thrombotic Risk in CAD

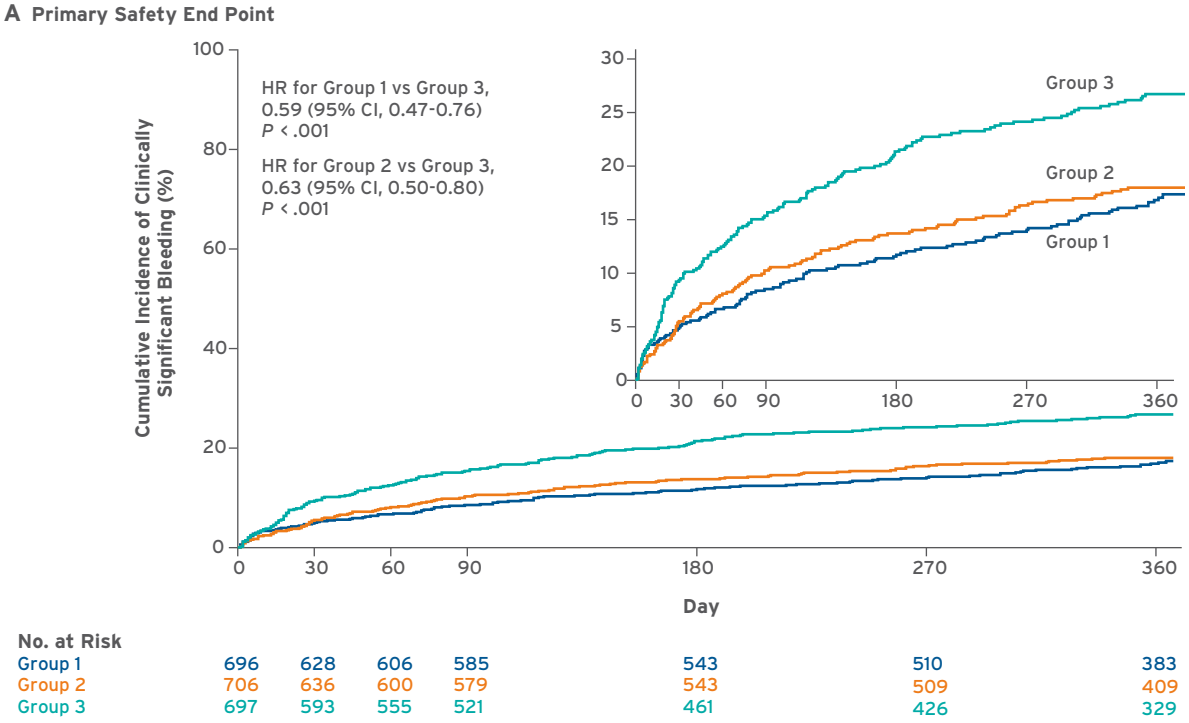
Despite optimum medical therapy, the recurrent event rate in post-acute coronary syndrome (ACS) in trials remains high (about 10% in the first year). This is even higher in clinical practice, with up to one-third of elderly, high-risk patients having a recurrent event in the first year post-ACS. The protective role of high density lipoproteins (HDL) has been questioned based on human genetic studies and negative clinical trial results of various HDL raising therapies. In contrast, recent genetic analyses support the causality of triglyceride-rich lipoproteins in CV risk. According to Peter Libby, MD, Brigham & Women's Hospital, Boston, Massachusetts, USA, the dependent and independent variable in adjusting the CV risk of triglycerides for HDL may have been confused [Libby P et al. *Eur Heart J*. 2014]; it may be the case that HDL is in fact a marker for triglycerides. These findings may aid in achieving biomarker-guided personalisation of the management of risk in secondary prevention by targeting residual low-density lipoprotein (LDL) risk, residual inflammatory risk, and residual risk due to triglyceride-rich lipoproteins.

Role of PCSK9 Inhibition Still Evolving

Inhibition of PCSK9 is effective in reducing LDL, in patients with familial hypercholesterolemia and in very high-risk patients. PCSK9 monoclonal antibodies may also be useful in managing ACS, as ACS induces increased PCSK9 levels, which in turn may influence plaque vulnerability of the coronary vessels [Navarese EP et al. *Ann Int Med*. 2016]. The FOURIER study [Sabatine MS et al. *N Engl J Med*. 2017] showed a 1.5% absolute risk reduction (RR) with evolocumab on time to CV death, myocardial infarction (MI), stroke, hospitalisation for unstable angina, or coronary revascularisation in very high-risk patients who used the highest tolerated dose of statins (HR, 0.85; 95% CI, 0.79 to 0.92; $P < .001$). The ODYSSEY trial [Steg PG et al. ACC Conference 2018], which assessed alirocumab, also showed a reduction in LDL-cholesterol (LDL-C) and CV endpoints. The study included an even higher-risk group of patients and longer follow-up than the FOURIER study, demonstrating a 15% RR in major adverse cardiovascular events (MACE; HR, 0.85; 95% CI, 0.78 to 0.93; $P = .0003$) and a 1.6% absolute risk reduction. The EVOlocumab study for early reduction of LDL-C levels in patients with ACSs [EVOPACS; NCT03287609] is currently investigating the safety and efficacy of evolocumab in ACS patients.

Other methods to reduce LDL-C are being investigated, including inclisiran, a RNA interference therapeutic inhibiting the synthesis of PCSK9, which was found to lower PCSK9 and LDL-C levels in patients at high CV risk with elevated LDL cholesterol levels [Ray KK et

Figure 1. Clinically Significant Bleeding in PIONEER AF-PCI



Reprinted from *The New England Journal of Medicine*. Gibson MC et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI;375:2423-34. Copyright © 2016 Massachusetts Medical Society.

al. *N Engl J Med*. 2017]. However, there are still some unanswered questions, according to François Mach, MD, Geneva University Hospital, Switzerland. These include the need for more data regarding inclisiran and other silencing drugs, whether PCSK9i could be of use in patients with chronic kidney disease, and the clinical effect of PCSK9i on Lp(a) reduction. The benefits of PCSK9 inhibitors are clear, Prof. Mach stated, they offer the possibility of treating patients 1 or 2 times a month, with most patients (95%) reaching target levels with minimal side effects. However, long-term follow-up data is still needed and cost is an issue. Nevertheless, PCSK9 inhibition is a promising therapy.

Preventing CV Events by Targeting Residual Inflammatory Risk

Paul M. Ridker, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data from the CANTOS trial, which included more than 10,000 patients. First presented at the European Society of Cardiology Congress 2017, CANTOS demonstrated large dose-dependent reductions in C-reactive protein (CRP) with no change in LDL-C and high-density lipoprotein cholesterol [Ridker PM et al. *N Engl J Med*. 2017]. In the secondary endpoint analysis, it was found that those with greater high-sensitivity (hs)CRP reduction had a greater risk reduction of MACE [Ridker PM et al. *Lancet*. 2018]. Interestingly, the reduction of MACE in patients with moderate chronic kidney disease (n = 1,875) was also significant (HR, 0.82; 95% CI, 0.68 to 1.00; *P* = .05) [Ridker PM et al. *J Am Coll Cardiol*. 2018]. New data suggest that residual inflammatory risk is still present irrespective of on-treatment LDL-C (including patients with LDL-C < 20 mg/dL) and is associated with increased rates of adverse events (Figure 1) [Bohula EA et al. *Circulation*. 2018].

Figure 1. Presence of Residual Inflammatory Risk in Patients with hsCRP < 1, 1-3, and > 3

		LDL-C at 1 month (mg/dL)				
		< 20	20-49	50-69	70-99	≥ 100
Incidence rate at 3 years	hsCRP < 1 mg/L	9.0%	9.8%	10.4%	10.9%	12.3%
	hsCRP 1-3 mg/L	10.8%	12.0%	12.6%	13.2%	14.9%
	hsCRP > 3 mg/L	13.1%	14.7%	15.4%	16.4%	18.2%

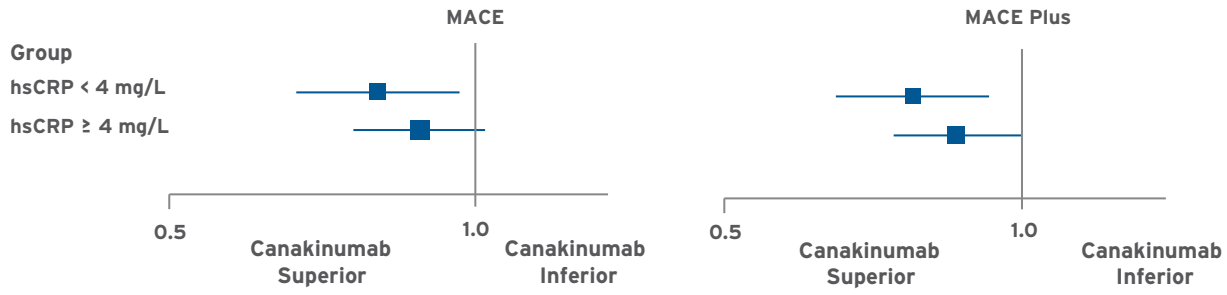
LDL-C, low-density lipoprotein cholesterol

Profound LDL reduction without inflammation effects is very effective, as is profound inflammation effects without LDL reduction, Dr Ridker stated. There are two important questions to answer for evidence-based guidelines: is there consistent evidence that the biomarker independently predicts risk, and is there randomised trial proof that lowering the biomarker lowers the risk? The confirming answer to the first question concerns many biomarkers, whereas the second answer only applies to LDL-C/ApoB and hsCRP/IL-6 [Ridker PM et al. *J Am Coll Cardiol*. 2018; in press].

Optimised Antithrombotic Strategy Post-ACS: Which Option?

When optimising antithrombotic strategy in high-risk, post-ACS patients, two periods can be distinguished: the time between discharge and 1 year post-ACS, and the time beyond 1 year post-ACS. For the early post-ACS period, dual antiplatelet therapy (DAPT; aspirin plus clopidogrel) is the gold standard. Optimisation may be achieved by using stronger $P2Y_{12}$ inhibition; providing an ischaemic benefit, but also a higher bleeding risk [Wiviott SD et al. *N Engl J Med*. 2007; Wallentin L et al. *N Engl J Med*. 2009]. A second option is to add Factor Xa inhibition to standard of care [Mega JL et al. *N Engl J Med*. 2012]. As Thomas Cuisset, MD, CHU TIMONE,

Figure 1. CANTOS: Consistency of Effect



Adapted from Ridker PM et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*. 2018;391:319-28.

Marseille, France, pointed out, the gold standard as of August 2018 is to use more potent $P2Y_{12}$ inhibitors (e.g., prasugrel, ticagrelor). Current guidelines state that triple therapy with aspirin plus clopidogrel and low-dose rivaroxaban is possible in patients with low bleeding risk.

Beyond the first year post-ACS, the gold standard has been lifelong single antiplatelet therapy after discontinuation of DAPT. Clinicians now have two options to add to aspirin; the PEGASUS trial [Bonaca MP et al. *N Engl J Med*. 2015] investigated ticagrelor and the COMPASS trial [Eikelboom J et al. *N Engl J Med*. 2017] assessed rivaroxaban in patients with stable coronary artery disease or peripheral arterial disease.

The first option to optimise antithrombotic strategy is prolonged $P2Y_{12}$ inhibition, which in itself consists of various options. The second option is to add Factor Xa inhibition to aspirin. Prof. Cuisset explained that a 2-step approach is required, although this can be challenging. Firstly, candidates for an optimised strategy would need to be identified (i.e., high/low bleeding risk), and secondly, the best strategy should be selected for each patient based on individual patient characteristics. Still, a number of issues may arise, such as the risk of nonadherence in case of multiple treatment changes, the duration of the chosen optimised strategy (30 months, 3 years or lifetime?), the choice of long-term DAPT and whether monotherapy with new $P2Y_{12}$ blockers is feasible.

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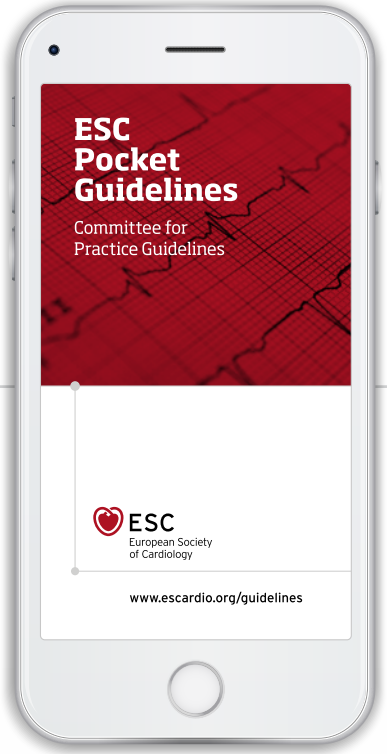

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